Motofen® (Difenoxin and Atropine Sulfate Tablets) for Management of Acute Nonspecific Diarrhea and Acute Exacerbations of Chronic Functional Diarrhea

**Background**
With the acquisition of Motofen® (difenoxin and atropine sulfate tablets) by Sebela Pharmaceuticals Inc. and its reintroduction to the market, the clinical data supporting Motofen may not be familiar to many healthcare providers. Motofen is approved for adjunctive therapy in the management of acute nonspecific diarrhea and acute exacerbations of chronic functional diarrhea. 1

**Methods**
Relevant data from the following studies will be reviewed.
- Clinical studies conducted for FDA approval of Motofen that are now on file with Sebela Pharmaceuticals Inc.
- Data from prescribing information for both Motofen and Lomotil® (diphenoxylate hydrochloride and atropine sulfate tablets)

**Dosage Information**
Each Motofen tablet contains 1 mg difenoxin and 0.025 mg atropine sulfate. Motofen is a schedule IV controlled substance. It contains a subtherapeutic dose of atropine sulfate to discourage deliberate overdose. 3

Motofen dosing in adults:
- Initial dose: 2 tablets
- 1 tablet after each loose stool or every 3 to 4 hours as needed
- Do not exceed 8 tablets in any 24-hour period

**No Metabolism for Active Drug**
Motofen contains the active metabolite, difenoxin, and does not need to be converted in the liver. Motofen is rapidly and extensively absorbed, reaching peak plasma levels in 40 to 60 minutes (Figure 1). 1

**Peak Plasma Level**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Plasma concentration (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>60</td>
<td>5</td>
</tr>
</tbody>
</table>

*After a Motofen dose of 2 mg, the approximate peak plasma level of 160 ng/mL was reached. Motofen reached an approximate peak plasma level of 163 ng/mL after a 10 mg dose.  
Approximately the same peak plasma level was obtained for both drugs (Figure 1), however, the Motofen dosage was one-fifth that of Lomotil. Studies have shown that difenoxin is five times as potent as diphendoxylate with a similar side effect profile. 3*

**Acute Nonspecific Diarrhea**

*Figure 2: Time to last liquid stool after initial dose*

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>25</td>
</tr>
<tr>
<td>5-9</td>
<td>20</td>
</tr>
<tr>
<td>10-14</td>
<td>15</td>
</tr>
<tr>
<td>15-19</td>
<td>10</td>
</tr>
<tr>
<td>20-24</td>
<td>5</td>
</tr>
</tbody>
</table>

57% of patients had their last liquid stool in 4 hours or less after an initial 2 mg dose of Motofen (Figure 2). 1

**Control of Acute Exacerbations of Chronic Functional Diarrhea**

*Figure 4: Reliable relief for patients with chronic functional diarrhea*

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Motofen</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>58%</td>
<td>26%</td>
</tr>
<tr>
<td>48</td>
<td>57%</td>
<td>36%</td>
</tr>
</tbody>
</table>

More than half of the patients experienced statistically significant control of diarrhea by day 2 of treatment with Motofen (Figure 4). 1 Control of diarrhea was consistently maintained at day 4 of treatment. 1

**Adverse Events**

<table>
<thead>
<tr>
<th>Event</th>
<th>Motofen (n=38)</th>
<th>Placebo (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Epigastric distress</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Constipation</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>CNS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Headache</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Headache</td>
<td>2.5%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Tiredness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervousness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Most common adverse events associated with Motofen

**Conclusion**
Motofen does not have to be metabolized into an active form and it is rapidly and extensively absorbed into the bloodstream. Motofen provides relief of acute nonspecific diarrhea rapidly within 4 hours of the initial dose for more than half (57%) of patients. It controls diarrhea within the first 24 hours for 79% of patients and within 48 hours for 92% of patients. In acute exacerbations of chronic functional diarrhea, Motofen provides relief for more than half of patients by day 2 and consistently maintains relief at 4 days of treatment. The most common adverse events for Motofen (>2%) are nausea, vomiting, dry mouth, dizziness and light-headedness, drowsiness, and headache. Constipation was reported in <1% of patients, indicating that it produces an antidiarrheal effect without causing constipation often seen with other antidiarrheal agents.

**Important Safety Information**
**Indications and Usage**
Motofen is indicated as adjunctive therapy in the management of acute nonspecific diarrhea and acute exacerbations of chronic functional diarrhea.

**Contraindications**
Motofen is contraindicated in patients with diarrhea associated with organisms that penetrate the intestinal mucosa (bacterial E. coli, Salmonella species, Shigella and pseudomembranous colitis associated with broad spectrum antibiotics.

Motofen is also contraindicated in children under 2 years of age, in patients with known hypersensitivity to difenoxin, atropine, or any of the inactive ingredients, and in patients who are jaundiced.

**Warnings**
Motofen is not an innocuous drug and dosage recommendations should be strictly adhered to. Overdose may result in severe respiratory depression and coma, possibly leading to permanent brain damage or death.

The use of Motofen does not preclude the administration of appropriate fluid and electrolyte therapy. Dehydration, particularly in children, may further influence the variability of response to Motofen and may predispose to delayed diarrhea intoxication. Drug-induced inhibition of peristalsis may result in fluid retention in the colon, and this may further aggravate dehydration and electrolyte imbalance.

Use with caution in patients with ulcerative colitis or liver or kidney disease. Motofen may produce drowsiness or dizziness. Use caution when engaging in activities requiring mental alertness, such as driving or operating dangerous machinery.

Keep out of reach of children.

Please see full Prescribing Information on reverse or at www.motofen.com

**References**
**DESCRIPTION**
Each five-sided, blue MOTOFEN® tablet contains: 1 mg of difenoxin (equivalent to 0.95 mg of difenoxin hydrochloride) and 0.23 mg of atropine sulfate (equivalent to 0.01 mg of atropine). Difenoxin hydrochloride, 1-(p-quin-3,3-diphenylacetyl)-4-phenyl-4-piperidincarboxylic acid monohydrochloride, is an orally administered anticholinergic agent which is chemically related to the narcotic meperidine.

The structural formula is:

![Structural formula of Difenoxin](image)

Difenoxin sulfate is present to discourage deliberate overdoses. Atropine sulfate, an anticholinergic, is benzeneacetic acid, 4-methyl-4-azabicyclo[3.2.1]octan-8-yl ester, endo-(±)-, (2:1) (salt), monohydrate and has the following structural formula:

![Structural formula of Atropine](image)

**CLINICAL PHARMACOLOGY**
Animal studies have shown that difenoxin hydrochloride manifests its antidiarrheal effect by slowing intestinal motility. The mechanism of action is by a local effect on the gut-intestinal wall. Difenoxin is the principal active metabolite of diphenoxylate.

Following oral administration of MOTOFEN®, difenoxin is rapidly and extensively absorbed. Mean peak plasma levels of approximately 0.16 ng/ml were observed, from 40 to 60 minutes in most patients following an oral dose of 2 mg. Plasma levels decline to below 10% of their peak values within 24 hours and to less than 1% of their peak values within 72 hours. This decline parallels the appearance of difenoxin and its metabolites in the urine. Difenoxin is metabolized to a less active metabolite. Both the drug and its metabolites are excreted, mainly as conjugates, in urine and feces.

**INDICATIONS AND USAGE**
MOTOFEN® is indicated as adjunctive therapy in the management of acute nonspecific diarrhea and acute exacerbations of chronic functional diarrhea.

**CONTRAINDICATIONS**
MOTOFEN® is contraindicated in patients with diarrhea associated with organisms that cause the inflammatory bowel disease (Crohn, ulcerative colitis) and Shigella, Salmonella species, Shigella and pseudomembranous colitis associated with broad spectrum antibiotics. Antiperistaltic agents should penetrate the intestinal mucosa (toxigenic MOTOFEN® is metabolized to an inactive hydroxylated metabolite. Both the drug and its metabolites are in most patients following an oral dose of 2 mg. Plasma levels decline to less than 10% of the initial peak levels. Difenoxin was first used in patients with acute ulcerative colitis to inhibit the adrenergic neurons and reduce urinary retention. In patients with acute ulcerative colitis, the patient should be carefully observed and MOTOFEN® therapy should be discontinued promptly if abdominal distention occurs or if other untoward symptoms develop.

MOTOFEN® should be used with extreme caution in patients with advanced hepatic disease and in all patients with abnormal liver function tests since hepatic coma may be precipitated.

Atropine—a subtherapeutic dose of atropine has been added to difenoxin hydrochloride to discourage deliberate overdosage. Usage of MOTOFEN® in recommended doses is not likely to cause prominent anticholinergic side effects, but MOTOFEN® should be avoided in patients in whom anticholinergic drugs are contraindicated. The warnings and precautions for use of anticholinergic agents should be observed in children, signs of atropinism may occur even in whom anticholinergic drugs are contraindicated.

MOTOFEN® is indicated as adjunctive therapy in the management of acute nonspecific diarrhea and acute exacerbations of chronic functional diarrhea.

**PRECAUTIONS**
Caution to Patients: INCREASED SENSITIVITY TO ANTIDIARRHEAL AGENTS DURING PREGNANCY. The medication should be kept out of reach of children since accidental poisoning in children, possibly leading to severe respiratory depression and coma, is a recognized hazard from the accidental ingestion of this medication. Therefore, keep this medication out of the reach of children. The use of MOTOFEN® is contraindicated in children under 2 years of age.

**DOSEAGE AND ADMINISTRATION**
The recommended starting dosage of MOTOFEN® tablets in adults is 2 tablets taken 1 tablet every 3 hours. MOTOFEN® is continued as tolerated until the clinical response is noted. The usual adult dosage is 2 tablets every 3 to 4 hours as needed, but the total dosage during any 24-hour treatment period should not exceed 8 tablets. In the treatment of diarrhea, if clinical improvement is not observed in 48 hours, continued administration of this type of treatment is not recommended. For acute diarreal and acute exacerbations of functional diarrhea, treatment beyond 48 hours is usually not necessary. Studies in children below the age of 12 have been inadequate to evaluate the safety and effectiveness of MOTOFEN® in this age group. MOTOFEN® is contraindicated in children under 2 years of age.

**HISTORY**
MOTOFEN® is available as a white, five-sided, scored tablet with “502” on the concave face and “4” on the other side. Each tablet contains 1 mg difenoxin and 0.025 mg atropine sulfate. Supplied in bottles of 100 tablets (NDC 54766-230-1), Store at 20°C-25°C (68°-77°F) [See USP Controlled Room Temperature].

**Pediatric Use**
SAFETY AND EFFECTIVENESS IN CHILDREN BELOW THE AGE OF 12 HAVE NOT BEEN ESTABLISHED. MOTOFEN® is contraindicated in children under 2 years of age. See OVERDOSAGE section for information on hazards from accidental poisoning in children.

**ADVERSE REACTIONS**
In view of the small amount of atropine present (0.025 mg/tablet), such effects as dryness of the skin and mucous membranes, flushing, hyperthermia, tachycardia and urinary retention are very unlikely to occur, except perhaps in children.

Many of the adverse effects reported during clinical investigation of MOTOFEN® are difficult to distinguish from symptoms associated with the diarrheal syndrome. However, the following events were reported at the stated frequencies:

Shigelosusis: Nausea, 1 in 15 patients; vomiting, 1 to 30 patients; dry mouth, 1 to 3 patients; epigastric distress, 1 in 100 patients; and cramps, 1 in 20 patients.

Central Nervous System: Dizziness and light headache, 1 to 20 patients; drowsiness, 1 in 25 patients; and headache, 1 in 40 patients; tiredness, nervousness, insomnia and confusion ranged from 1 in 200 to 1 in 600 patients.

Other infrequent reactions: Burning eyes and altered vision occurred in a few cases.

The following adverse reactions have been reported in patients receiving chemically-related drugs: numbness of extremities, erythema, depression, sedation, anaphylactic, anaphylactoid, urticaria, swelling of the gums, pruritus, toxic megacolon, paralytic ileus, pancreatitis, and anemia.

This medication should be kept out of the reach of children since accidental poisoning in children, possibly leading to severe respiratory depression and coma, is a recognized hazard from the accidental ingestion of this medication.

**DRUG ABUSE AND DEPENDENCE**
MOTOFEN® tablets are Schedule IV controlled substances. Addiction to dependence on difenoxin hydrochloride is theoretically possible at high dosage. Therefore, the recommended dosage should not be exceeded. Because of the structural and pharmacological similarities of difenoxin hydrochloride to drugs with a definite addiction potential, MOTOFEN® should be administered with considerable caution to patients who are receiving addicting drugs, to individuals known to be addiction prone, or to those in whom addiction potential may increase dosage on their own initiative.

**OVERDOSAGE**
**Diagnosis and Treatment**
In the event of overtreatment (initial signs may include dryness of the skin and mucous membranes, flushing, hyperthermia and tachycardia followed by lethargy or coma. Hypotonic, reflexes, mydriasis, pinpoint pupils and respiratory depression) gastric lavage, establishment of a patent airway and possibly mechanically assisted respiration are advised. The narcotic antagonistic naloxone may be used in the treatment of respiratory depression caused by narcotic analogues of pharmacologically related compounds such as MOTOFEN® tablets. Naloxone is administered intravenously, the onset of action is generally apparent within two minutes. Naloxone may be administered subcutaneously or intramuscularly providing a slightly less rapid onset of action but a more prolonged effect.

To counteract respiratory depression caused by MOTOFEN® overdosage, the following dosages schedule for naloxone should be followed:

**Adult Dosage**
The usual initial adult dose of naloxone is 0.4 mg (one ml) administered intravenously. If respiratory function does not adequately improve after the initial dose, the same dose may be repeated at two to three minute intervals. Children: The usual adult dose of naloxone for children is 0.01 mg/kg body weight administered intravenously and repeated at two to three minute intervals if necessary.

Since the duration of action of difenoxin hydrochloride is longer than that of naloxone, the patient should be observed for 30 hours later.

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