Summary of Product Characteristics (SmPC)

1 Name of the Medicinal Product

Product Name: Bisacodyl Tablets BP (Laxidyl)

2 Quality and Quantitative Composition

1 Qualitative Declaration:

Each enteric coated tablet contains:
Bisacodyl BP 5 mg.

2.2 Quantitative Declaration:

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Ingredients</th>
<th>Pharmacopoeial Status</th>
<th>Qty (Mg/Tab)</th>
<th>Purpose For Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLEND</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Bisacodyl</td>
<td>BP</td>
<td>5</td>
<td>Active</td>
</tr>
<tr>
<td>2</td>
<td>Starch (Maize)</td>
<td>NF</td>
<td>19.825</td>
<td>Diluent</td>
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<td>3</td>
<td>Lactose</td>
<td>BP</td>
<td>44.865</td>
<td>Diluent</td>
</tr>
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<td>BINDER</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Starch (Maize)</td>
<td>NF</td>
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<td>Binder</td>
</tr>
<tr>
<td>5</td>
<td>Methylparaben</td>
<td>BP</td>
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<td>Propylparaben</td>
<td>BP</td>
<td>0.015</td>
<td>Preservative</td>
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<tr>
<td>7</td>
<td>Purified water</td>
<td>BP</td>
<td>---</td>
<td>Binding Solvent</td>
</tr>
<tr>
<td>LUBRICATION</td>
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<td></td>
</tr>
<tr>
<td>8</td>
<td>Magnesium Stearate</td>
<td>BP</td>
<td>1.00</td>
<td>Lubricant</td>
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<td>9</td>
<td>Sodium Starch Glycolate (Type A)</td>
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<td>2.00</td>
<td>Lubricant</td>
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<td>10</td>
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<td>0.080</td>
<td>Antioxidant</td>
</tr>
<tr>
<td>11</td>
<td>Butylated Hydroxytoluene</td>
<td>BP</td>
<td>0.080</td>
<td>Antioxidant</td>
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<td>COATING</td>
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</tr>
<tr>
<td>12</td>
<td>Tabcoat TCE yellow (SCE 7014)</td>
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<td>9.00</td>
<td>Coating agent</td>
</tr>
<tr>
<td>13</td>
<td>Acetone</td>
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<td>Coating Solvent</td>
</tr>
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<td>14</td>
<td>Isopropyl Alcohol</td>
<td>BP</td>
<td>0.0460 ml</td>
<td>Coating Solvent</td>
</tr>
</tbody>
</table>

3 Pharmaceutical Form

Visual Description: Yellow colored, round, biconvex, enteric coated tablet.
4 Clinical Particulars

4.1 Therapeutic Indication:

Constipation either chronic or of recent onset.
Bowel Clearance before surgery, labour or radiological investigation.

4.2 Posology and Method of Administration:

The tablets should not be crushed or chewed but swallowed whole with water. It is recommended to take the coated tablets at night to have a bowel movement the following morning.
The coated tablets should not be taken together with products which reduce the acidity of the upper gastrointestinal tract, such as milk, antacids or proton pump inhibitors, in order not to prematurely dissolve the enteric coating.

Short-term treatment of constipation:
Adults and children over 10 years: 1 to 2 coated tablets (5-10 mg) daily before bedtime
Children 4-10 years: 1 coated tablet (5 mg) daily before bedtime
In the management of constipation, once regularity has been restarted dosage should be reduced and can usually be stopped.
In preparation for radiological investigation, and preoperatively:
Should only be used under medical supervision.
Adults and children over 10 years: 2 coated tablets (10 mg) in the morning and 2 coated tablets (10 mg) in the evening and 1 suppository (10 mg) on the following morning is recommended
Children 4-10 years: 1 coated tablet (5 mg) in the evening and 1 suppository (5 mg) on the following morning is recommended
When using Bisacodyl to prepare the patient for radiographic examination of the abdomen or employing it preoperatively, tablets should be combined with suppositories in order to achieve complete evacuation of the intestine.

4.3 Contraindication:

In patients with ileus, intestinal obstruction, acute surgical abdominal conditions like acute appendicitis, acute inflammatory bowel diseases, and in severe dehydration.
Bisacodyl is also contraindicated in patients with known hypersensitivity to substances of the triarylmethane group.

4.4 Special warning and precautions for use:

Bisacodyl should not be taken on a continuous daily basis for more than 5 days without investigating the cause of constipation.
Prolonged use can precipitate the onset of an atomic non-functioning colon.
Prolonged excessive use may lead to fluid and electrolyte imbalance and hypokalaemia.
Intestinal loss of fluids can promote dehydration. Symptoms may include thirst and oliguria. In patients suffering from fluid loss where dehydration may be harmful (e.g. renal insufficiency, elderly patients) Bisacodyl should be discontinued and only be restarted under medical supervision.
Patients may experience haematochezia (blood in stool) that is generally mild and self-limiting.
Dizziness and/or syncope have been reported in patients who have taken Bisacodyl. The details available for these cases suggest that the events would be consistent with defecation syncope (or syncope attributable to straining at stool), or with a vasovagal response to abdominal pain related to the constipation, and not necessarily to the administration of Bisacodyl itself. There have been isolated reports of abdominal pain and bloody diarrhoea occurring after taking Bisacodyl. Some cases have been shown to be associated with colonic mucosal ischaemia. Bisacodyl should not be taken by children under 10 years without medical advice. Patients with rare hereditary problems of galactose/fructose intolerance, Lapp lactase deficiency or glucose/galactose malabsorption or sucrose- isomaltase insufficiency should not take this medicine.

**Pregnancy and lactation:**
As with all medicines, Bisacodyl should not be taken in pregnancy, especially the first trimester, and during breast feeding unless the expected benefit is thought to outweigh any possible risk and only on medical advice.

**4.5 Interaction with other medicinal products and other forms of interactions:**

The concomitant use of diuretics or adrenocorticosteroids may increase the risk of electrolyte imbalance if excessive doses of bisacodyl are taken. Electrolyte imbalance may lead to increased sensitivity to cardiac glycosides. The concomitant use of antacids and milk products may reduce the resistance of the coating of the tablets and result in dyspepsia and gastric irritation.

**4.6 Fertility, Pregnancy and lactation**

**Pregnancy and lactation:**
As with all medicines, Bisacodyl should not be taken in pregnancy, especially the first trimester, and during breast feeding unless the expected benefit is thought to outweigh any possible risk and only on medical advice.

**4.7 Effects on ability to drive and use machine:**
No studies on the effects on the ability to drive and use machines have been available.

**4.8 Undesirable effects:**

**Undesirable side effects:**
Adverse events have been ranked under headings of frequency using the following convention: Very common (≥1/10); common (≥1/100, < 1/10); uncommon (≥1/1000, <1/100); rare (≥1/10000, <1/1000); very rare (<1/10000).

**Not known** – incidence cannot be estimated from the available data.

**Immune system disorders:**

- **Rare**: Hypersensitivity
- **Not known**: Anaphylactic reactions, angioedema

**Metabolism and nutrition disorders:**

- **Not known**: Dehydration

**Gastrointestinal disorders**

- **Common**: Abdominal pain, abdominal cramps, nausea and diarrhoea.
- **Uncommon**: Vomiting, haematochezia (blood in stool), abdominal discomfort, anorectal discomfort.
- **Not known**: Colitis

**4.9 Overdose:**
**Overdose**

*Symptoms:*
If high doses are taken watery stools (diarrhoea), abdominal cramps and a clinically significant loss of fluid, potassium and other electrolytes can occur. Laxatives when taken in chronic overdose may cause chronic diarrhoea, abdominal pain, hypokalaemia, secondary hyperaldosteronism and renal calculi. Renal tubular damage, metabolic alkalosis and muscle weakness secondary to hypokalaemia have also been described in association with chronic laxative abuse.

*Therapy:*
After ingestion of oral forms of Bisacodyl, absorption can be minimised or prevented by inducing vomiting or gastric lavage. Replacement of fluids and correction of electrolyte imbalance may be required. This is especially important in the elderly and the young. Administration of antispasmodics may be of some value.

5. **Pharmacological Properties**

5.1 **Pharmacodynamic Properties:**

   **ATC Code:** A06AB02 (Laxidyl)

   **Mechanism of Action**
   LAXIDYL is a contact stimulant laxative, administered either orally or rectally, which acts directly on the colonic mucosa to produce normal peristalsis throughout the large intestine. LAXIDYL is poorly absorbed, if at all, in the small intestine following oral administration. On contact with the mucosa or submucosal plexi of the large intestine, LAXIDYL stimulates sensory nerve endings to produce parasympathetic reflexes resulting in increased peristaltic contractions of the colon. It has also been shown to promote fluid and ion accumulation in the colon, which increases the laxative effect. A bowel movement is usually produced approximately 6 hours after oral administration (8-12 hours if taken at bedtime).

5.2 **Pharmacokinetic properties:**

   LAXIDYL is a contact stimulant laxative, administered either orally or rectally, which acts directly on the colonic mucosa to produce normal peristalsis throughout the large intestine. LAXIDYL is poorly absorbed, if at all, in the small intestine following oral administration. On contact with the mucosa or submucosal plexi of the large intestine, LAXIDYL stimulates sensory nerve endings to produce parasympathetic reflexes resulting in increased peristaltic contractions of the colon. It has also been shown to promote fluid and ion accumulation in the colon, which increases the laxative effect. A bowel movement is usually produced approximately 6 hours after oral administration (8-12 hours if taken at bedtime).
5.3 Preclinical Safety data


Effects of the adenosine A1-receptor antagonist on defecation, small intestinal propulsion and gastric emptying in rats.

Suzuki M, Tomaru A, Kishibayashi N, Karasawa A.

Abstract

We examined the effects of 1,3-dipropyl-8-cyclopentylxanthine (DPCPX) and (R)-7,8-dihydro-8-ethyl-2-(3-noradamantyl)-4-propyl-1H-imidazo[2,1-i]purin-5(4H)-one (KF20274), selective adenosine A1-receptor antagonists, on the gastrointestinal propulsion in rats, as compared with those of the laxative bisacodyl. DPCPX and KF20274 (p.o.) dose-dependently increased the fecal pellet output, whereas these drugs at the dose that increased defecation did not affect small intestinal propulsion or gastric emptying. Bisacodyl increased defecation and slowed gastric emptying without any influence on small intestinal propulsion. Bisacodyl, but not DPCPX or KF20274, induced diarrhea at the dose inducing defecation. The present results suggest that the adenosine A1-receptor antagonist selectively enhances the lower gastrointestinal propulsion, resulting in defecation without diarrhea.
Effect of colchicine and bisacodyl on rat intestinal transit and nitric oxide synthase activity.

Karmeli F, Stalnikowicz R, Rachmilewitz D.

Abstract

BACKGROUND: Bisacodyl and colchicine affect smooth-muscle contractility, intestinal water, and electrolyte transport. Nitric oxide (NO) stimulates intestinal electrolyte secretion and has an important role as a mediator of intestinal motility. We therefore studied, in rats, the effects of these agents on nitric oxide synthase (NOS) activity and gastrointestinal transit.

METHODS: Rats were treated with bisacodyl (10 mg/kg intragastrically) or colchicine (5 mg/kg intraperitoneally) with or without pretreatment with ketotifen (1 mg/kg intragastrically). Rats were killed after 1, 2, and 4 h. The intestine was isolated and rinsed, the mucosa scraped, and NOS activity determined. In all rats small-intestinal transit was measured 15 min after intragastric administration of charcoal.

RESULTS: Bisacodyl (10 mg/kg) and colchicine (5 mg/kg) induced a significant decrease in jejunal NOS activity. Pretreatment with the mast cell stabilizer ketotifen, which has been shown to attenuate the increased permeability induced by NO inhibition, prevented the decrease in colonic and jejunal NOS activity induced by bisacodyl and colchicine. Bisacodyl and colchicine significantly decreased intestinal transit time. Their effect on transit time was similar to that induced by intravenous administration of NG-nitro-L-arginine methyl ester (10 mg/kg).

CONCLUSIONS: It is suggested that the effect of bisacodyl and colchicine on intestinal transport is, at least partly, mediated through NO inhibition.
Phenolphthalein and bisacodyl: assessment of genotoxic and carcinogenic responses in heterozygous p53 (+/-) mice and syrian hamster embryo (SHE) assay.

Stoll RE, Blanchard KT, Stoltz JH, Majeska JB, Furst S, Lilly PD, Mennear JH.

Abstract

Phenolphthalein (800 and 2400 mg/kg/day by gavage and 2400 mg/kg/day by diet) and bisacodyl (800-500, 4000-2000, and 8000 mg/kg/day by gavage) were administered to 15 male and 15 female and 20 male and 20 female p53(+/-) mice respectively for 26 weeks to investigate the potential carcinogenicity of each compound. Toxicokinetic analyses confirmed systemic exposure. p-Cresidine was administered by gavage (400 mg/kg/day) and served as the positive control agent in each study. Dietary phenolphthalein reduced survival in both sexes and early deaths were attributed to thymic lymphoma. No bisacodyl-related neoplasms were observed. Regardless of route of administration to p53(+/-) mice, phenolphthalein but not bisacodyl was unequivocally genotoxic, causing increased micronuclei in polychromatic erythrocytes. In the Syrian hamster embryo (SHE) cell transformation assay, phenolphthalein caused increases in morphologically transformed colonies, thereby corroborating NTP's earlier reports, showing phenolphthalein has potential carcinogenic activity. Bisacodyl was negative in the SHE assay. Results of these experiments confirm an earlier demonstration that dietary phenolphthalein causes thymic lymphoma in p53(+/-) mice and show that (1) phenolphthalein causes qualitatively identical results in this transgenic model regardless of route of oral administration, (2) phenolphthalein shows evidence of micronucleus induction in p53(+/-) mice for up to 26 weeks, (3) phenolphthalein induced transformations in the in vitro SHE assay, and (4) bisacodyl in p53(+/-) mice induces neither drug-related neoplasm, nor micronuclei in polychromatic erythrocytes, and did not induce transformations in the in vitro SHE assay.
Relationship between bisacodyl-induced urolithiasis and rat urinary bladder tumorigenesis.

Toyoda K, Imaida K, Shirai T, Imazawa T, Takahashi M.

Abstract

Dietary supplementation with bisacodyl at concentrations ranging from 1 to 0.3% was found to induce both calculi and epithelial proliferative lesions, including a transitional-cell carcinoma, in the urinary bladder of F344/DuCrj rats. In order to clarify the relationship between the bisacodyl-associated urinary bladder calculi and the development of proliferative lesions in the urinary bladder, male and female rats were administered bisacodyl-diets at concentrations of 0.3, 0.1, and 0.03% for 32 wk. Both sexes of animals treated with bisacodyl suffered from diarrhea throughout the experimental period. Epithelial proliferative lesions and calculus formation were observed only in the urinary bladder of male rats given the 0.3% bisacodyl diet. Proliferative lesions and increases of bromouracil deoxyriboside (BUdR) labeling indices were found only in the urinary bladder epithelium of rats with calculi, the severity of the former correlating with the calculus weight and being most marked in the dome areas, which are susceptible to physical stimulation. These findings indicate a close relationship between the development of proliferative lesions and the existence of calculi in the urinary bladder, and suggest that bisacodyl-induced proliferative lesions are not caused directly by bisacodyl per se but are secondary to calculus formation.
6 Pharmaceutical Particulars

6.1 List of Excipient:

<table>
<thead>
<tr>
<th>Sr No.</th>
<th>Name of Ingredient</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Starch (Maize)</td>
</tr>
<tr>
<td>2</td>
<td>Lactose</td>
</tr>
<tr>
<td>3</td>
<td>Methylparaben</td>
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<td>Sodium Starch Glycolate (Type A)</td>
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<td>Butylated Hydroxytoluene</td>
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<td>Tabcoat TCE yellow (SCE 7014)</td>
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<tr>
<td>11</td>
<td>Acetone</td>
</tr>
<tr>
<td>12</td>
<td>Isopropyl Alcohol</td>
</tr>
</tbody>
</table>

6.2 Incompatibilities:

Not Applicable

6.3 Shelf life:

3 Years

6.4 Special precautions for storage:

Store below 30°C, protected from light.

6.5 Nature and contents of container:

10 x 10 Blister Pack: 174 mm Printed Aluminium Foil, 178 mm bottom foil

6.6 Special precaution for disposal (and other handling)

Not applicable

7 Marketing Authorization Holder: Troikaa Pharmaceuticals Limited.

8 Marketing Authorization Numbers: TB/01/3364

9 Date of authorization: 04/10/2007
10 Date of revision of the text: NA

11. Dosimetry: Not applicable

12. Instruction for preparation of radiopharmaceuticals: Not applicable