

PRODUCT MONOGRAPH

Pr**DICETEL**[®]

(Pinaverium Bromide)

50 mg & 100 mg film-coated tablets

Gastrointestinal calcium antagonist

BGP Pharma ULC
85 Advance Road
Etobicoke, Ontario
M8Z 2S6

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THERAPEUTIC CLASSIFICATION

Gastrointestinal calcium antagonist

CLINICAL PHARMACOLOGY

DICETEL[®] (pinaverium bromide) is a calcium antagonist which inhibits the calcium influx by blocking the voltage-dependent calcium channel at the smooth muscle cell level. It possesses a high degree of selectivity for the intestinal smooth muscle. ^{5,7,19,32,36,48,50}

Many studies showed that pinaverium bromide induces a relaxation of the gastrointestinal and the biliary tracts and mainly of the colon, an inhibition of the motor colonic response to food and/or pharmacological stimulations, implying the action of the drug in irritable bowel syndrome. ^{4,9,37,47}

INDICATIONS AND CLINICAL USE

DICETEL[®] (pinaverium bromide) is indicated:

- for the treatment and relief of symptoms associated with irritable bowel syndrome (IBS): abdominal pain, bowel disturbances and intestinal discomfort.
- for the treatment of symptoms related to functional disorders of the biliary tract.

CONTRAINDICATIONS

DICETEL[®] (pinaverium bromide) is contraindicated in patients with known hypersensitivity to pinaverium bromide or any of the excipients.

No other contraindications have been identified at this time.

WARNINGS

Contact of **DICETEL**[®] (pinaverium bromide) with the oesophageal mucosa may be irritating. Therefore, it is strongly recommended that the tablet be taken with a glass of water during mealtime. The tablet must be swallowed without being chewed or sucked. If more than three tablets are prescribed per day, the additional tablet(s) should be taken concurrently with a glass of water and a snack.

Because of a risk of oesophageal lesions, instructions on the method of administration of **DICETEL** should be carefully adhered to (see above and **ADVERSE REACTIONS**). Patients with pre-existing oesophageal lesion and/or hiatus hernia should pay special attention to the correct method of administration of **DICETEL**.

The safety and efficacy of **DICETEL** have not been established in children and experience is limited. Therefore, **DICETEL** is not recommended for use in children.

PRECAUTIONS

DICETEL[®] (pinaverium bromide) should not be administered for the relief of motility dysfunction due to underlying organic disease.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medication.

Use in pregnancy:³

There are no adequate data from the use of pinaverium bromide in pregnant women. Animal studies are insufficient with respect to effects on pregnancy, embryonal/ fetal development, parturition and/ or postnatal development. The potential risk for humans is unknown. The safety of **DICETEL** during pregnancy has not been established. Consequently, in the pregnant patient, this drug should only be administered if, in the judgement of the physician, its use is essential to the welfare of the patient.

Furthermore, the presence of bromine should be taken into account. Theoretically, administration of pinaverium bromide at the end of the pregnancy can affect the new-born neurologically (hypotony, sedation). No such cases however have been reported with **DICETEL**.

Use during lactation:

There is insufficient information on the excretion of **DICETEL** in human or animal breast milk. Physico-chemical and available pharmacodynamic/ toxicological data on **DICETEL** point to excretions in breast milk and a risk to the suckling infant cannot be excluded. **DICETEL** should not be used during breast-feeding.

ADVERSE REACTIONS

Minor adverse events were reported and listed as mild and moderate. They were mainly minor digestive disorders that may be related to the disease, such as epigastric pain and/or fullness (0.8%), nausea (0.5%), constipation (0.4%), heartburn (0.3%), distension (0.3%), diarrhoea (0.2%).⁸

For other systems: headache (0.3%), dryness of the mouth (0.3%), drowsiness (0.2%), vertigo (0.2%) and skin allergy (0.2%).

Post-Market Adverse Drug Reactions

The following adverse reactions have been reported spontaneously during post-marketing use. A precise frequency cannot be estimated from available data (not known).

Gastrointestinal disorders

Gastrointestinal disturbances have been observed, e.g. abdominal pain, vomiting, and dysphagia.

Oesophageal lesion may occur when advised method of administration of **DICETEL** is not followed (see **WARNINGS**).

Skin and subcutaneous tissue disorders

Cutaneous effects have been observed, e.g. rash, pruritus, urticaria, and erythema.

Immune system disorders

There have been spontaneous reports of systemic hypersensitivity reactions involving the subcutaneous tissue and other organ systems of the body such as angioedema and anaphylactic shock.

DRUG INTERACTIONS

Clinical trials have demonstrated the absence of any interaction between pinaverium bromide and digitalis drugs, oral anti-diabetics, insulin, oral anticoagulants and heparin.

Co-administration of an anticholinergic drug may enhance spasmolysis.

No interference with laboratory tests for drug level detection was observed.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

In man, apart from diarrhoea and/or flatulence, **DICETEL**[®] (pinaverium bromide) induced no undesirable effects in daily dosages of up to 1,200 mg.^{41,42}

No cases of overdose of **DICETEL** have been reported to date. No specific antidote is known. However, if overdose occurs, symptomatic treatment is recommended.

DOSAGE AND ADMINISTRATION

The usual adult dosage is 50 mg three times a day (total daily dose of 150 mg). The dosage may be increased up to a maximum of 100 mg taken three times a day (maximum total daily dose of 300 mg).

It is recommended that the tablet be taken with a glass of water during meals or snacks. The tablet should not be swallowed when in the lying position or just before bedtime.

The duration of treatment depends on the disorders for which **DICETEL** is given.

AVAILABILITY

DICETEL[®] (pinaverium bromide) is available as:

50 mg Film-coated Tablets: Each round, biconvex, yellowish-orange-coloured, film-coated tablet contains 50 mg of pinaverium bromide as active ingredient. The tablet is engraved with “50” on one side. Available in blister packs, in boxes of 100 tablets (4 strips of 25 tablets).

100 mg Film-coated Tablets: Each round, biconvex, yellowish-orange-coloured, film coated tablet contains 100 mg of pinaverium bromide as active ingredient. The tablet is engraved with “100” on one side. Available in blister packs, in boxes of 100 tablets (5 strips of 20 tablets).

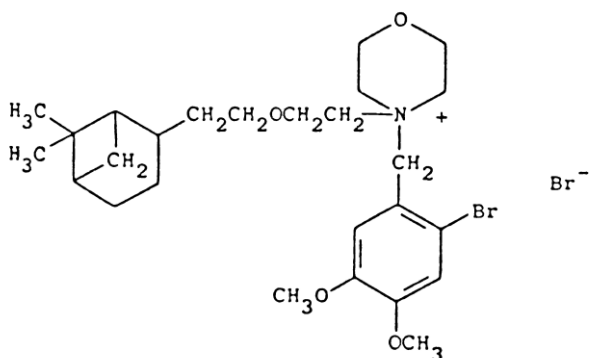
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper name: pinaverium bromide

Chemical name: 4-(6-bromoveratryl)-4-[2-[2-(6,6-dimethyl-2-norpinyloxy)ethoxy]ethyl]-morpholinium bromide.

Structural formula:



Molecular formula: C₂₆H₄₁Br₂NO₄

Molecular weight: 591.42

Description:

Pinaverium bromide is a white, fine, crystalline powder, slightly soluble in distilled water, practically insoluble in ether, but very soluble in 96% alcohol. The melting range determined by means of Mettler FP apparatus is 152° to 158°C.

COMPOSITION

Film-coated Tablets: In addition to pinaverium bromide, 50 mg and 100 mg per tablet,

DICETEL contains the following excipients:

- in the core: microcrystalline cellulose, pre-gelatinized starch, lactose monohydrate, anhydrous colloidal silica, talc and magnesium stearate;
- in the film coating: basic butylated methacrylate copolymer, sodium laurylsulphate, stearic acid, talc, hydroxypropyl methylcellulose, iron oxide yellow, iron oxide red.

STABILITY AND STORAGE RECOMMENDATIONS

The stability of **DICETEL** film-coated tablets has been demonstrated in blister packaging alone and in blister packs inserted in the dispensing box. **DICETEL** should be stored at room temperature (15°C to 30°C).

Pr **DICETEL[®] Information for the Patient**
(Pinaverium bromide)
Film-coated Tablets
Gastrointestinal calcium antagonist

BGP Pharma ULC
85 Advance Road
Etobicoke, Ontario
M8Z 2S6

This information provides a summary on DICETEL and explains how to use it. For more information or advice, please ask your doctor or pharmacist.

What is DICETEL[®]?

DICETEL is the brand name for the medication, pinaverium bromide. It is available as a round, biconvex, yellowish-orange film-coated tablet containing either 50 mg or 100 mg of pinaverium bromide. The 50 mg tablets are engraved with “50” on one side and are 8 mm in diameter. The 100 mg tablets are engraved with “100” on one side and are 11 mm in diameter. In addition, the tablets also contain the following nonmedicinal ingredients: microcrystalline cellulose, pre-gelatinized starch, lactose monohydrate, anhydrous colloidal silica, talc and magnesium stearate, basic butylated methacrylate copolymer, sodium laurylsulphate, stearic acid, hydroxypropyl methylcellulose, iron oxide yellow, iron oxide red.

If you are allergic to any of these substances ask your doctor or pharmacist whether these ingredients may pose a problem.

How does DICETEL[®] work?

DICETEL works by relaxing the muscles in the walls of the gut (also called the intestine). DICETEL treats and relieves the symptoms associated with irritable bowel syndrome (IBS) such as abdominal pain, bowel disturbances (constipation and/or diarrhea) and intestinal discomfort (bloating).

What you should tell your doctor before you take DICETEL[®]:

- If you are pregnant or breast-feeding. DICETEL should not be used during breastfeeding.
- If you have any allergies or have had a reaction to any of the ingredients in DICETEL (see What is DICETEL?).
- If you are lactose intolerant, talk to your doctor, as this product contains lactose.
- If you have been told by your doctor that you have a rare condition of intolerance to some sugars or difficulty absorbing some sugars (galactose intolerance, Lapp lactase deficiency or glucose/ galactose malabsorption), do not take this medicinal product before talking to your doctor, as the product contains lactose.
- If you have lesions or damage to your esophagus, including hernia (rupture) affecting the esophagus.

- If you have other medical conditions and/ or are taking other medications.

How to take DICETEL[®] tablets:

- Take only as directed by your doctor. The dose-range for adults is DICETEL 50 - 100 mg three times a day.
- To avoid irritation to your esophagus (food pipe), the tablet should be swallowed whole with a glass of water during meals; do not crush, chew or suck the tablet.
- The tablet should not be swallowed when in the lying position or just before bedtime.
- DICETEL is not recommended for use in children.

What if you miss a dose?

If you miss the usual time for taking a DICETEL tablet, take it as soon as possible. If however, it is near the time of your next dose, skip the missed pill and return to your usual dosing schedule. Do not take double the dose.

What if you take too many tablets?

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Never change the amount of DICETEL you are taking unless instructed to do so by your doctor. If you have taken more DICETEL tablets than the recommended dose, tell a doctor immediately. Show the doctor your pack of tablets.

What are possible side effects with DICETEL[®]?

Most people tolerate DICETEL well. Like any other medicine, however, DICETEL may cause side effects in some people. These tend to be mild when they occur. Some people may feel stomach pain and/or fullness, abdominal pain, nausea, vomiting, difficulty swallowing, constipation, heartburn, bloating or diarrhea. Since these side effects are similar to the symptoms of IBS, it may be hard to tell the difference. Other side effects include headache, dryness of the mouth, drowsiness, dizziness, skin allergy, rash, itching, hives, redness of skin and allergic reactions. Lesions or damage to the esophagus may occur if DICETEL tablets are not taken as instructed. If you get these or any other problems while you are taking DICETEL, consult your doctor or pharmacist.

Looking after your tablets.

- Store at room temperature (15°C to 30°C).
- Keep away from children.
- Don't take your tablets if they are past their expiry date.

Remember that this medication has been prescribed for you. Do not share your medications with others, even if they are experiencing similar symptoms. Only a doctor can prescribe DICETEL.

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PHARMACOLOGY

ANIMAL PHARMACOLOGY

In vitro and *in vivo* animal studies have shown that **DICETEL**[®] (pinaverium bromide) has a spasmolytic effect in the gastrointestinal tract, as supported by a clearly demonstrated Ca⁺⁺ antagonistic mechanism of action. It acts on the calcium influx by blocking the voltage-dependent calcium channel. Its selectivity of action has been established with validated models. ^{6,7,10,13,19,34}

Animal studies demonstrated that pinaverium bromide possesses potent spasmolytic properties on intestinal smooth muscle and very weak anticholinergic effects observed at high dosage. There is no noticeable cardiovascular effect. ¹²

Radiolabelled pinaverium bromide was poorly absorbed (5 to 10%) after oral administration (a solution of 2.46 mg/kg, corresponding to 50 FCi/kg) to rats. The radioactivity was rapidly taken up by the liver and excreted in the bile. There was no noticeable enterohepatic cycle and only 5% of the biliary radioactivity was reabsorbed after oral dosing. ^{5,28,29}

CLINICAL PHARMACOLOGY

Several studies have shown that pinaverium bromide induces the following effects: oesophageal, gastric and duodenal relaxation; acceleration of gastric emptying; colonic and intestinal relaxation; inhibition of motor colonic response to a meal; reduction or inhibition of colonic response to stimulation by neostigmine; reduction of gall bladder contractions, of Oddi's sphincter phasic contractions, of endocholedochal pressure and of retention index during scintigraphy. ^{4,9,15,20,24,31,36,37,40,46,47}

Other more recent studies (doses up to 1.2g) showed that pinaverium bromide did not affect the cardiovascular system nor have any anticholinergic side effects. ^{4,9,23,27,39} In particular, two clinical studies carried out with the injectable formulation (total dose of 2 or 4 mg corresponding to a 50 mg oral dose) demonstrated that pinaverium bromide did not influence sinoatrial, atrioventricular, intraventricular conduction, or atrial excitability. It also exhibited no antiarrhythmic properties. ^{25,26}

Administered to patients with glaucoma in a placebo-controlled study, pinaverium bromide did not interfere with the ocular parameters of glaucoma patients: acuity and visual field, ocular tonus measure at aplanation and especially intraocular pressure.³⁹

Various investigators studied total or segmental intestinal transit time by different techniques in healthy volunteers or in patients. Pinaverium bromide does not increase transit time; it either has no effect or decreases transit time, especially in constipated patients.^{4,9,23}

Recent clinical data have confirmed the effects of pinaverium bromide on the lower gastrointestinal tract.

A four-centre, double-blind, double-dummy, crossover, randomized study grouped 86 out-patients of both sexes, suffering from irritable bowel syndrome. Patients received either three **DICETEL** tablets or capsules daily for 19 days. The major symptoms of irritable bowel syndrome were studied separately: pain, bowel disturbances and distension. Pinaverium bromide tablets were shown to be equivalent to the capsules; the tablet was however better tolerated.^{16,35} In addition, the long-term safety and tolerance of the tablet at a dose of 3 tablets/day for a duration of 3 to 9 months was demonstrated.¹⁷

Three other studies have confirmed the action of pinaverium bromide in irritable bowel syndrome.^{20,24,37}

PHARMACOKINETICS

The pharmacokinetic profile of orally administered pinaverium bromide is a very important feature in explaining its selectivity of action on the gastrointestinal tract.

Following administration of an oral solution to animals (2.46 mg/kg) and humans (50 mg) pinaverium bromide was poorly absorbed (5 to 10%) due to its highly polar quaternary ammonium group and its high molecular weight.^{44,45} *In vitro* studies have shown that pinaverium bromide is highly bound to both animal and human plasma proteins (97%).²⁸ The selective distribution in the digestive tract, low absorption, low enterohepatic cycle and almost

exclusive elimination in the feces are the main kinetic characteristics of pinaverium bromide following oral administration.

A kinetic single dose study was performed in 24 healthy volunteers receiving 4 mg intravenously or 100 mg (2 x 50 mg tablets) orally of non-radiolabelled pinaverium bromide. Maximum peak plasma levels were reached within one hour after oral dosing. The absolute bioavailability was very low after oral administration (less than 1%). The mean half-life of elimination is close to 1.5 hours for both routes of administration.¹⁴

Biotransformation

The metabolic pathway is characterized by demethylation of one of the methoxy groups, hydroxylation of the norpinanyl ring and elimination of the benzyl group with subsequent opening of the morpholine ring.¹¹

Interference With Other Drugs

Various studies were carried out to investigate the possible interaction with drugs usually prescribed for long-term use; digitalis, digoxin, oral antidiabetics, insulin, oral anticoagulants and heparin.^{18,49} No drug interactions nor interference with laboratory tests for drug level detection were observed.

TOXICOLOGY

ACUTE TOXICITY

The results of acute toxicity studies performed in various species using different routes of administration are as follows:²²

LD₅₀ (Swiss mouse)

P.O. 1531 mg/kg	(20 animals/dose)
I.P. 41 mg/kg	(20 animals/dose)
S.C. 436 mg/kg	(5 animals/dose)
I.V. 62 mg/kg	(20 animals/dose)

LD₅₀ (Wistar rat)

P.O. 1145 mg/kg	(20 animals/dose)
I.P. 36 mg/kg	(20 animals/dose)

LD₅₀ (rabbit)

P.O. 154 mg/kg	(6 animals/dose)
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Safety studies were conducted in conscious Beagle dogs to whom a single oral dose of 50 mg/kg pinaverium bromide was administered. No changes were observed in the body temperature or in the cardiovascular parameters.

LONG-TERM TOXICITY

Wistar rats were treated daily for two months with 25 to 50 mg/kg/day of pinaverium bromide administered by an intragastric catheter. No clinical, biological or histological signs of intolerance were observed and no deaths occurred.

A three-month tolerance study was conducted in the Sprague-Dawley rat using doses of 250, 500 and 1000 mg/kg/day of pinaverium bromide administered in the diet. At doses of 500 and 1000 mg/kg/day, anorexia, weight loss and liquid feces were observed. No other signs of clinical, biological or histological toxicity were detected and no deaths occurred.

Similarly, a fifty-two week oral toxicity study conducted with pinaverium bromide in the Sprague-Dawley rat demonstrated that, under the experimental conditions, the minimal toxic dose in the rat was in the range of 100 - 300 mg/kg/day when administered in the diet.

An oral chronic study in the dog indicated that administration of pinaverium bromide at doses of 10 and 25 mg/kg/day for 6 months did not cause any toxic signs. At doses of 25 and 50 mg/kg/

day for 13 months, pinaverium bromide caused a decreased weight gain in the treated animals relative to the controls; however, no significant haematological modifications were observed.

Reproductive and Developmental Toxicology

Fertility studies in rats

Pinaverium was administered to male rats 10 weeks before mating. The doses of 50 mg/kg and 150 mg/kg had no effects on fertility. In a second study pinaverium was administered from the day of mating until day 20 post gestation at the doses of 10, 25 and 50 mg/kg. Pregnancy rate in the 50 mg/kg dose group was decreased (60% versus 90-100% in the control, 10 and 25 mg/kg groups), with a higher number of sterile females, and a higher number of placental resorptions.

Teratology Study in the Rat

During a teratology study, 4 groups of 20 Wistar albino rats received 10, 25 or 50 mg/kg/day of pinaverium bromide by means of a gastric catheter. Drug administration was performed 6 days a week, from the day of conception to the 18th day of gestation.³

Results indicated that for the high dose group (50 mg/kg/day) the number of fertilized females was slightly lower and the numbers of sterile females and resorptions were higher when compared to placebo. The lower doses groups (10 and 25 mg/kg/day) did not differ significantly from placebo.

None of the fetuses or young of treated females from any dose group exhibited anatomical anomalies. Up to 30 days post-birth, neither development nor behaviour modifications were observed in the offspring. Pinaverium bromide was not considered teratogenic in the rat under the experimental conditions of the study.

Teratology Study in the Rabbit

Doses of 2.5, 5 and 10 mg/kg/day of pinaverium bromide were administered 6 days per week, from day 6 to day 18 of gestation to 4 groups of 10 Russian albino rabbits.³

None of the fetuses from the mothers treated with pinaverium bromide showed any visceral or skeletal abnormalities. The number of resorptions, the mean number of fetuses, and the

percentage of abortions were not significantly different at any of the dose levels administered. Under these experimental conditions, pinaverium bromide did not demonstrate a teratogenic effect in the rabbit.

MUTAGENICITY

Pinaverium bromide has no mutagenic potential as illustrated by the negative results obtained in tests for chromosomal mutation (i.e., micronucleus test in mice for pinaverium bromide administered by various routes) and for chromosomal aberrations on human lymphocytes-genic mutation (i.e., two Ames tests, mouse lymphoma assay).^{1,2,21,30,38,43}

These results were also confirmed in the cell transformation test on embryonic lung cells of Syrian hamsters (SHE cells).³³

Carcinogenicity

In the carcinogenicity study in mice doses of 30, 120 and 480 mg/kg were administered in food for 111 weeks. The benign and malignant tumors observed in the treated and control groups were typical of the strain and age of the animals; their frequency in the treated and control groups was the same. Pinaverium, was not considered having carcinogenic potential in mice under the experimental conditions of the study.

Carcinogenicity in rats was studied over 126 weeks with initial dose levels at 20, 60 and 180 mg/kg. After 13 weeks of dosing the doses of 60 and 180 mg were increased to 80 and 320 mg/kg, respectively. The number of tumors recorded in all animals was in line with that expected for rats of this strain and age. Frequency of spontaneous tumors was not increased, except for leukemias in the mid-dose group, which was considered to be unrelated to treatment, because no increase was observed in the high dose group. It was concluded that pinaverium has no carcinogenic potential in rats under the test conditions of the study.

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