Colchicine Benta®

Colchicine

FORMS AND PRESENTATION

Colchicine Benta®: Film coated tablets: Box of 30

COMPOSITION

Colchicine Benta®: Each film coated tablet contains colchicine 1mg.

Excipients: Lactose monohydrate, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, hypromellose, titanium dioxide, polyethylene glycol.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: drugs for gout, with no effect on uric acid metabolism.

ATC code: M04AC01

In the AGREE (Acute Gout Flare Receiving Colchicine Evaluation) study, low- and high-dose colchicine were compared using a randomized, placebo-controlled design. The high-dose prolonged colchicine regimen (4.8 mg total over 6 hours) was compared with a placebo and a low-dose abbreviated regimen (1.8 mg total over 1 hour, i.e. 1.2 mg followed by 0.6 mg in 1 hour). Both colchicine regimens were significantly more effective than placebo, with 32.7% responders in the high dose group, 37.8% responders in the low-dose group, and 15.5% responders in the placebo group (P = 0.034 and P = 0.005, respectively, versus placebo). The results at the primary 24-hour endpoint demonstrate superior safety of low dose colchicine, without loss of efficacy, relative to high dose colchicine for early acute gout flare (self-administered within 12 hours of flare onset). The pharmacokinetic analysis performed in this study showed that the colchicine plasma concentration was decreased substantially from about 12 hours after administration in healthy volunteers.

Colchicine prophylaxis (0.6 mg twice daily) during initiation of allopurinol for chronic gout arthritis reduced the frequency and severity of acute flares and reduced the likelihood of recurrent flares. Treatment may be continued for up to 6 months, based on clinical data. Prospective randomized controlled trials are needed to further evaluate flare prophylaxis for up to 6 months, after 6 months, and over time.

The mechanism of action of colchicine in the treatment of gout is not clearly understood. Colchicine is considered to act against the inflammatory response to urate crystals, by possibly inhibiting the migration of granulocytes into the inflamed area. Other properties of colchicine, such as interaction with the microtubules, could also contribute to the operation. The onset of action is approximately 12 hours after oral administration and is maximal after 1 to 2 days.

Pharmacokinetic properties

Colchicine is rapidly and almost completely absorbed after oral administration. Maximum plasma concentrations are met usually after 30 to 120 minutes. The terminal half-life is 3 to 10 hours. Plasma protein binding is approximately 30%. Colchicine is partially metabolized in the liver and then in part via the bile. It accumulates in leucocytes. Colchicine is largely excreted (80%) in unchanged form and as metabolites in the faeces. 10-20% is excreted in the urine.

Renal impairment:

Colchicine is significantly excreted in the urine in healthy subjects. Clearance of colchicine is decreased in patients with impaired renal function. Total body clearance of colchicine was reduced by 75% in patients with end-stage renal disease undergoing dialysis.

The influence of renal impairment on the pharmacokinetics of colchicine was assessed in a study in patients with familial Mediterranean fever (FMF), 5 women and 4 men, with (n=4) and without (n=5) renal impairment. The mean age was 30 years (range 19-42 years). All 5 patients with renal impairment had biopsy-proven amyloidosis; 4 were on routine hemodialysis and 1 had a serum creatinine CL of 15 ml/min. They could therefore be classified as having severe renal impairment. Subjects received 1 mg colchicine except for 1 subject with cirrhosis who received 500 micrograms. A 4-fold decrease in colchicine CL was observed in subjects with renal impairment compared to those with normal renal function (0.168 ± 0.063 l/h/kg vs. 0.727 ± 0.110 l/h/kg). The terminal half-life was 18.8 ± 1.2 h for subjects with severe renal impairment and 4.4 ± 1.0 h for those with normal renal function. The volume of distribution was similar between groups. The patient with cirrhosis had a 10-fold lower CL compared to the subjects with normal renal function.

INDICATIONS

Adults

Colchicine Benta® is used for the treatment of acute gout. It is also used for the prophylaxis of recurrent gout and to prevent acute attacks during the initial treatment with allopurinol or uricosuric drugs.

Pediatric population

Colchicine Benta® is indicated in Familial Mediterranean Fever for prophylaxis of attacks and prevention of amyloidosis.

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients
- Patients with blood dyscrasias
- Pregnancy
- Breastfeeding
- Women of childbearing potential unless using effective contraceptive measures
- Patients with severe renal impairment
- Patients with severe hepatic impairment
- Colchicine should not be used in patients undergoing hemodialysis since it cannot be removed by dialysis or exchange transfusion
- Colchicine is contraindicated in patients with renal or hepatic impairment who are taking a P-glycoprotein (P-gp) inhibitor or a strong CYP3A4 inhibitor.

PRECAUTIONS

Colchicine is potentially toxic so it is important not to exceed the dose prescribed by a physician with the necessary knowledge and experience.

Colchicine has a narrow therapeutic window. The administration should be discontinued if toxic symptoms such as nausea, vomiting, abdominal pain, diarrhea occur.

Colchicine may cause severe bone marrow depression (agranulocytosis, aplastic anemia, thrombocytopenia). The change in blood counts may be gradual or very sudden. Aplastic anemia in particular has a high mortality rate. Periodic checks of the blood picture are essential.

If patients develop signs or symptoms that could indicate a blood cell dyscrasia, such as fever, stomatitis, sore throat, prolonged bleeding, bruising or skin disorders, treatment with colchicine should be immediately discontinued and a full hematological investigation should be conducted straight away.

Caution is advised in case of:

- liver or renal impairment
- cardiovascular disease
- gastrointestinal disorders
- elderly and debilitated patients
- patients with abnormalities in blood count

Patients with liver or renal impairment should be carefully monitored for adverse effects of colchicine.

Co-administration with P-gp inhibitors and/or moderate or strong CYP3A4 inhibitors will increase the exposure to colchicine, which may lead to colchicine induced toxicity including fatalities. If treatment with a P-gp inhibitor or a moderate or strong CYP3A4 inhibitor is required in patients with normal renal and hepatic function, a reduction in colchicine dosage or interruption of colchicine treatment is recommended.

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 medicine.

DRUG INTERACTIONS

Colchicine has been shown to induce reversible malabsorption of vitamin B12, apparently by altering the function of ileal mucosa. Colchicine may impair the absorption of fat, sodium, potassium, nitrogen, xylose and other actively transported sugars. This may lead to decreased serum cholesterol and carotene concentrations.

Colchicine is inhibited by acidifying agents but is potentiated by alkalinizing agents.

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Colchicine may increase sensitivity to CNS depressants and enhance the response to sympathomimetic agents.
Colchicine may cause false-positive results when testing urine for RBC or hemoglobin.
Colchicine may react with cyclosporin leading to an increased risk of nephrotoxicity and increased plasma-cyclosporin concentration.
Colchicine has been reported to interfere with urinary determinations of 17-hydroxycorticoids using the Reddy, Jenkins and Thorn procedure.
Concomitant use with clarithromycin may lead to colchicine toxicity. Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (P-gp). Clarithromycin and other macrolides are known to inhibit CYP3A and P-gp. When clarithromycin and colchicine are administered together, inhibition of P-gp and/or CYP3A by clarithromycin may lead to increased exposure to colchicine. Patients should be monitored for clinical symptoms of colchicine toxicity.
Concomitant use with erythromycin may also lead to colchicine toxicity.

ADVERSE EFFECTS

Colchicine therapy may cause elevated alkaline phosphatase and SGOT values.
Decreased thrombocyte values may be obtained during therapy.
Bone marrow depression with aplastic anemic, agranulocytosis, leukopenia or thrombocytopenia may occur in patients receiving long term therapy. Loss of hair, rashes, vesicular dermatitis, peripheral neuritis or neuropathy, myopathy, anuria, renal damage, hematuria and purpura have been reported with prolonged administration of colchicine.
Vomiting, diarrhea, abdominal pain and nausea may occur, especially when maximum doses are necessary for a therapeutic effect. These may be particularly troublesome in the presence of peptic ulcer or spastic colon.
At toxic doses colchicine may cause severe diarrhea, generalized vascular damage and renal damage with hematuria and oliguria. To avoid more serious toxicity, discontinue use when these symptoms appear, regardless of whether joint pain has been relieved.
Dermatoses have been reported; hypersensitivity reactions may occur infrequently.
Hepatobiliary disorders: Hepatotoxicity can be observed although frequency is not known.

DOSAGE AND ADMINISTRATION

Adults:
Treatment of acute gout attack:
1 mg (1 tablet) to start followed by 500 micrograms (half a tablet) after 1 hour.
No further tablets should be taken for 12 hours.
After 12 hours, treatment can resume, if necessary, with a maximum dose of 500 micrograms (half a tablet) every 8 hours until symptoms are relieved.
The course of treatment should end when symptoms are relieved or when a total of 6 mg (6 tablets) has been taken.
No more than 6 mg (6 tablets) should be taken as a course of treatment.
After completion of a course, another course should not be started for at least 3 days (72 hours).
Prophylaxis of gout attack during initiation of therapy with allopurinol and uricosuric drugs:
500 micrograms (half a tablet) twice daily.
The treatment duration should be decided after factors such as flare frequency, gout duration and the presence and size of tophi have been assessed.
Patients with renal impairment:
Use with caution in patients with mild renal impairment. For patients with moderate renal impairment, reduce dose or increase interval between doses. Such patients should be carefully monitored for adverse effects of colchicine.
Patients with hepatic impairment:
Use with caution in patients with mild/moderate hepatic impairment. Such patients should be carefully monitored for adverse effects of colchicine.
Elderly:
Use with caution.
Method of Administration:
For oral administration: Tablets should be swallowed whole with a glass of water

OVERDOSAGE

Colchicine has a narrow therapeutic window and is extremely toxic in overdose. Patients at particular risk of toxicity are those with renal or hepatic impairment, gastrointestinal or cardiac disease, and patients at extremes of age.
Following colchicine overdose, all patients, even in the absence of early symptoms, should be referred for immediate medical assessment.
Clinical:
Symptoms of acute overdosage may be delayed (3 hours on average): nausea, vomiting, abdominal pain, hemorrhagic gastroenteritis, volume depletion, electrolyte abnormalities, leukocytosis, hypotension in severe cases.
The second phase with life threatening complications develops 24 to 72 hours after drug administration: multisystem organ dysfunction, acute renal failure, confusion, coma, ascending peripheral motor and sensory neuropathy, myocardial depression, pancytopenia, dysrhythmias, respiratory failure, consumption coagulopathy.
Death is usually a result of respiratory depression and cardiovascular collapse. If the patient survives, recovery may be accompanied by rebound leukocytosis and reversible alopecia starting about one week after the initial ingestion.
Treatment:
No antidote is available.
Elimination of toxins by gastric lavage within one hour of acute poisoning could be assessed.
Oral activated charcoal could be considered in adults who have ingested more than 0.1mg/kg body weight within 1 hour of presentation, and in children who have ingested any amount within 1 hour of presentation.
In this case, hemodialysis has no efficacy (high apparent distribution volume).
Close clinical and biological monitoring in a hospital environment is advisable.
Symptomatic and supportive treatment; control of respiration, maintenance of blood pressure and circulation, correction of fluid and electrolytes imbalance; is essential.
The lethal dose varies widely (7-65 mg single dose) for adults but is generally about 20 mg.

STORAGE CONDITIONS

Store below 30°C.
Keep in original pack in intact conditions.

Marketing Authorization Holder and Manufacturer
Benta S.A.L.
Dbayeh – Lebanon

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