

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use orBec® safely and effectively. See full prescribing information for orBec®.

orBec® (beclomethasone dipropionate) TABLETS

Initial U.S. approval: 200X

INDICATIONS AND USAGE

orBec® is an anti-inflammatory corticosteroid indicated for the treatment of graft versus host disease (GVHD) involving the gastrointestinal tract in conjunction with an induction course of high-dose prednisone or prednisolone (1)

DOSAGE AND ADMINISTRATION

orBec® is dosed as one immediate-release (IR) tablet plus one enteric-coated (EC) tablet, taken together four times daily for 50 days (2)

DOSAGE FORMS AND STRENGTHS

- Immediate-release (IR) tablet: 1 mg (3)
- Enteric-coated (EC) tablet: 1 mg (3)

CONTRAINDICATIONS

- Patients who cannot swallow tablets should not receive orBec® (4)

WARNINGS AND PRECAUTIONS

- orBec® is a corticosteroid medication that may suppress the immune system and the hypothalamic-pituitary-adrenal axis.

Prophylaxis of infections in patients who are receiving immunosuppressive medications may be necessary (5.1)

- Patients who have received treatment with orBec® may demonstrate adrenal hyporesponsiveness in situations involving medical and surgical stress (5.2)
- Clinical judgment should be exercised in patients who are taking orBec® along with other immunosuppressive drugs, as discontinuation of one or more immunosuppressive drugs may cause GVHD to worsen in intensity. Signs and symptoms that suggest recurrences of GVHD should be carefully evaluated, and if shown to be caused by GVHD, systemic immunosuppressive therapy may be required (5.3)

ADVERSE REACTIONS

Most common adverse reactions are endocrine disorders and HPA axis suppression (6)

To report SUSPECTED ADVERSE REACTIONS, contact DOR BioPharma Inc. at 305-534-3383 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

orBec® is not recommended for patients under six years of age (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised: X/200X

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

orBec® (oral beclomethasone dipropionate, BDP) is indicated for the treatment of graft vs host disease (GVHD) involving the gastrointestinal tract in conjunction with an induction course of high-dose prednisone or prednisolone. The safety and effectiveness of orBec® in treating GVHD has been demonstrated in patients whose symptoms included anorexia, nausea, vomiting, and diarrhea less than one liter per day. If a patient's symptoms might be caused by gastrointestinal infection rather than GVHD, the correct diagnosis should be obtained before therapy is begun.

Patients whose presentation suggests more severe GVHD (higher volume diarrhea, intestinal bleeding, abdominal pain, extensive skin GVHD, liver GVHD) are not candidates for a treatment approach that minimizes exposure to prednisone, prednisolone, or other potent immunosuppressive drugs.

The safety and efficacy of orBec® when prescribed for longer than 50 days have not been demonstrated.

2 DOSAGE AND ADMINISTRATION

orBec® is dosed as one immediate-release (IR) tablet plus one enteric-coated (EC) tablet, taken four times daily, with each tablet containing BDP 1 mg (two tablets taken four times daily, for a total of 8 mg BDP daily), taken for 50 days. The IR tablets are white rectangular tablets debossed with "IR" on one face and "BDP" on the other face. The EC tablets are white oval tablets printed with "EC" on one face in black ink.

orBec® therapy should be started simultaneously with an induction course of prednisone therapy at a dose of 1 mg/kilogram of body weight/day, for 10 days. If the patient's symptoms of GVHD have responded after 10 days of treatment, prednisone doses can be rapidly tapered over one week to physiologic replacement doses. In patients with a specific contraindication to prednisone therapy, for example, a fungal infection, psychosis, bone demineralization, or brittle diabetes,

orBec® may be prescribed without prednisone, based on data from uncontrolled clinical trials.

Small numbers of pediatric-age patients were included in clinical trials of orBec®, therefore experience is limited and dose-ranging studies have not been carried out. Caution is urged in administering orBec® to small children.

3 DOSAGE FORMS AND STRENGTHS

The following consists of one treatment and should be taken together:

- 1 mg immediate release (IR) rectangular tablet
- 1 mg enteric-coated (EC) oval tablet

4 CONTRAINDICATIONS

- Patients who cannot swallow tablets should not receive orBec® to ensure the integrity of the enteric coated tablet.

5 WARNINGS AND PRECAUTIONS

5.1 Immunosuppression

orBec® is a corticosteroid medication that may suppress the immune system and the hypothalamic-pituitary-adrenal axis. Possible signs of adverse reactions to orBec® include superficial fungal infections of the mouth and gastrointestinal tract, blood stream infections with bacteria and fungi, reactivation of viral infection, and adrenal insufficiency in response to stress. Prophylaxis of infections in patients who are receiving immunosuppressive medications may be necessary.

Clinical judgment should be exercised in patients who are taking orBec® along with other immunosuppressive drugs, as discontinuation of one or more immunosuppressive drugs may cause GVHD to worsen in intensity.

5.2 Adrenal hyporesponsiveness

Patients who have received treatment with orBec® may demonstrate adrenal hyporesponsiveness in situations involving medical and surgical stress. Anticipation of stress situations in a patient at risk should prompt consideration of stress coverage with glucocorticoids.

5.3 GVHD monitoring

orBec® should be prescribed only for patients in whom a diagnosis of gastrointestinal GVHD has been established and for whom a treatment regimen that minimizes prednisone exposure with the extended use of orBec® for 50 days is appropriate. While patients are taking orBec®, signs and symptoms that suggest recurrences of GVHD should be carefully evaluated, and if shown to be caused by GVHD, systemic immunosuppressive therapy may be required.

6 ADVERSE REACTIONS

In a medical situation where the disease being treated (gastrointestinal GVHD) and the treatment for the disease (immunosuppressive drugs) may both lead to morbidity and mortality, the most meaningful safety parameter in clinical trials of therapy for GVHD is mortality.

In the pivotal randomized placebo controlled phase 3 trial (Study ENT 00-02), a mortality benefit was shown for treatment with orBec®. In this highly complex and seriously ill patient population, adverse events (AEs), including serious adverse events (SAEs), were very common with adverse events being reported in essentially all patients in both orBec® and placebo groups, and serious adverse events being reported in approximately 40% of patients in both groups. Severe adverse events, adverse events attributed to study drug and adverse events leading to discontinuation of study drug were generally more common in the placebo group. Non-serious adverse events that resulted in discontinuation of study drug were more frequently reported in the placebo groups than in the orBec® group.

Adverse events were generally reported more frequently, or at an indistinguishably different rate, in the placebo group compared to the orBec® group, with the notable exception of endocrine disorders including the cushingoid diagnosis, which were reported more frequently in the orBec® group although both groups had received prednisone (19.7 vs. 23.0% respectively for endocrine disorders as a whole, $p=0.6708$ Fisher's exact test; 9.1 vs. 14.3% for the cushingoid

diagnosis, $p=0.4125$ Fisher's exact test). However, laboratory metabolic abnormalities associated with hypercortisolism such as hyperglycemia, hypokalemia and metabolic alkalosis were not reported as adverse events at different rates in the two groups, nor were blood glucose, potassium and serum bicarbonate values different between the groups.

Infections were more commonly reported as adverse events in the placebo group than in the orBec® group (60.6% vs. 50.8%, respectively, $p=0.2880$ Fisher's exact test).

Adverse events occurring in more than 10% of patients, with a numerically greater frequency in the orBec® treatment arm are listed in Table 1. Most are related to underlying GVHD.

Table 1. ENT 00-02 results: Adverse events occurring in $\geq 10\%$ of the patients in the orBec® group with a frequency numerically higher than in the placebo group.

Preferred term	Placebo N=66	orBec® N=61
graft versus host disease	27 (40.9 %)	26 (42.6 %)
fatigue	23 (34.8 %)	28 (45.9 %)
hypertension	23 (34.8 %)	24 (39.3 %)
bacteremia	13 (19.7 %)	14 (23.0 %)
hypokalaemia	14 (21.2 %)	13 (21.3 %)
hypocalcaemia	10 (15.2 %)	12 (19.7 %)
dizziness	10 (15.2 %)	11 (18.0 %)
erythema	8 (12.1 %)	13 (21.3 %)
hypophosphatemia	9 (13.6 %)	12 (19.7 %)
skin hyperpigmentation	10 (15.2 %)	10 (16.4 %)
cough	9 (13.6 %)	9 (14.8 %)
muscle cramp	6 (9.1 %)	11 (18.0 %)
pain in extremity	8 (12.1 %)	9 (14.8 %)
weight decreased	7 (10.6 %)	9 (14.8 %)
cushingoid	6 (9.1 %)	9 (14.8 %)
arthralgia	6 (9.1 %)	8 (13.1 %)
hyponatremia	7 (10.6 %)	7 (11.5 %)
osteopenia	7 (10.6 %)	7 (11.5 %)
tongue coated	5 (7.6 %)	7 (11.5 %)
dehydration	2 (3.0 %)	9 (14.8 %)
leukocytosis	4 (6.1 %)	7 (11.5 %)
hyperbilirubinemia	3 (4.5 %)	7 (11.5 %)
chest pain	1 (1.5 %)	7 (11.5 %)

Adverse events are coded using MedDRA (version 7).

Only treatment-emergent adverse events are summarized.

Preferred terms are sorted by descending order of frequency in the total column.

Subjects were counted only once for each preferred term.

Percentages are based on the number of subjects evaluable for safety in each treatment group.

A total of 129 subjects were randomized to receive oral BDP (n=62) or placebo (n=67). Two of these subjects, one from each treatment group, withdrew early from study before receiving any study medication. A total of 127 subjects were then considered evaluable for safety.

Two diagnoses were reported statistically significantly more frequently in the orBec® group than in the placebo group. These were dehydration (14.8% vs. 3.0%, $n=9$ vs. 2 respectively) and chest pain (11.5% vs. 1.5%, $n=7$ vs. 1 respectively). The reporting differences for dehydration do not appear to represent an actual difference in hydration status between groups as laboratory values reflective of hydration status (ie. serum BUN and total CO₂) are not different between groups. A similar analysis cannot be done for chest pain but the actual numbers are small enough to be consistent with a chance occurrence and no difference in cardiac events was seen between groups.

HPA axis suppression was more common in orBec® treated patients at Study Day 51 when compared to placebo patients, but only patients who were not treatment failures were evaluated. Treatment failure is defined as the requirement for additional corticosteroids over the doses prescribed by the protocol or the addition of another

immunosuppressive in response to uncontrolled GVHD during the 50-day treatment period. This demonstrates that there is some systemic effect of orBec® treatment that results in greater HPA suppression than in patients receiving only physiologic replacement of corticosteroids, however it fails to evaluate the overall risk of HPA suppression in the population as a whole because treatment failures were not evaluated. In the overall population, patients receiving orBec® had lower exposure to systemic corticosteroids suggesting that if this analysis were done, treatment with orBec® would probably not result in more HPA suppression.

In controlled trials, patients treated with orBec® had more frequent improvement in signs and symptoms of GVHD without requiring additional immunosuppressive agents, but more importantly had improved survival when compared with patients who did not receive orBec®. This consistent survival improvement is the strongest safety signal that can be seen in this high risk population. In summary, the use of orBec® in the treatment of gastrointestinal GVHD in allogeneic hematopoietic transplant patients is associated with a lower mortality, without evidence of a significant safety risk.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C: Like other corticosteroids, parenteral (subcutaneous) BDP was teratogenic and embryocidal in the mouse and rabbit when given at a dose of 0.1 mg/kg/day in mice or at a dose of 0.025 mg/kg/day in rabbits. These doses in mice and rabbits were approximately 1/16th the recommended daily oral dose in adults on a mg/m² basis.

There are no adequate and well-controlled studies in pregnant women. BDP should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

8.3 Nursing mothers

It is not known whether BDP or its metabolites 17-BMP or BOH, are excreted in human milk. Because other corticosteroids are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from BDP, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients below the age of 6 have not been established. orBec® is not recommended for patients under six years of age due to difficulties that small children may have in swallowing intact tablets.

8.5 Geriatric Use

Clinical studies of orBec® did not include sufficient numbers of subjects aged 65 and over to assess whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

10 OVERDOSAGE

There were no deaths over 15 days following the oral administration of a single dose of 3000 mg/kg in mice, 2000 mg/kg in rats, and 1000 mg/kg in rabbits. The doses in mice, rats, and rabbits were 1800, 2400, and 2400 times, respectively, the maximum recommended human daily dose on a mg/m² basis.

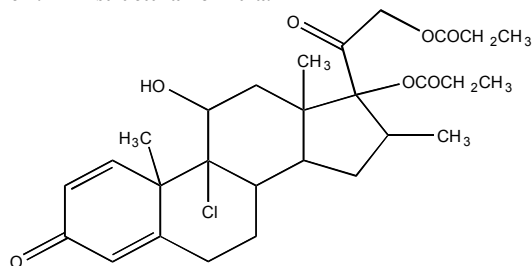
No data exist with regard to overdoses of orBec®. It is not anticipated that an overdose of orBec® would cause severe adverse reactions.

11 DESCRIPTION

Beclomethasone dipropionate (BDP), USP, the active component of orBec® immediate release tablets and enteric coated tablets, is an anti-inflammatory corticosteroid with the chemical name 9-chloro-11(beta),17,21-trihydroxy-16(beta)-methylpregna-1,4-diene-

3,20-dione 17,21-dipropionate. BDP is a diester of beclomethasone, a synthetic corticosteroid chemically related to dexamethasone. Beclomethasone differs from dexamethasone in having a chlorine at the 9-alpha carbon in place of a fluorine, and in having a 16 beta-methyl group instead of a 16 alpha-methyl group.

Figure 1: BDP structural formula.



BDP is a white or almost white, odorless powder with a molecular formula of C₂₈H₃₇ClO₇ and a molecular weight of 521.04. It is practically insoluble in water, freely soluble in acetone, sparingly soluble in alcohol.

The orBec® product is BDP formulated as 2 separate drug products intended to be taken simultaneously for oral administration: IR tablets, an immediate release (IR) tablet formulation, and EC tablets, an enteric coated (EC) tablet formulation. Each IR and EC tablet contains 1 mg BDP.

Inactive Ingredients, Tablet Core for Immediate Release and Enteric Coated Tablet: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, and magnesium stearate

Tablet Coating for Enteric Coated Tablet: methacrylic acid copolymer dispersion (Type C), triethyl citrate, polysorbate 80, silicon dioxide and sodium hydroxide

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of action

Following topical administration, BDP produces anti-inflammatory and vasoconstrictor effects. Corticosteroids have been shown to have a wide range of effects on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators involved in inflammation (e.g., histamine, eicosanoids, leukotrienes, and cytokines). Corticosteroid treatment of patients with GVHD is effective but the mechanisms of action of corticosteroids in this setting are not well known. They are presumed to involve blunting of inflammatory cytokine production by T cells in intestinal mucosa, inhibition of T cell-mediated apoptosis of epithelial cells, induction of apoptosis in activated effector T cells, and deviation of T cells responses toward tolerance or non-responsiveness. These effects of glucocorticoids might help to preserve integrity of the mucosal surface in GVHD, thereby reducing activation of innate immune mechanisms. The biological effects of BDP and its metabolites in intestinal mucosa are presumed to involve the same mechanisms as systemic glucocorticoids, that is, the suppression of immune-mediated events that result in damage to intestinal epithelium.

Based on biological and glucocorticoid receptor affinity assays, BDP has anti-inflammatory activity but it is also a pro-drug. It is hydrolyzed via esterase enzymes in intestinal mucosa and in the liver to the active metabolite beclomethasone-17-monopropionate (B-17-MP), which has high topical anti-inflammatory activity and strong glucocorticoid receptor binding *in vitro*.

Because corticosteroids are highly effective agents against both primary and recurrent GVHD, and because oral topical corticosteroids may allow reductions in prednisone exposure, thereby reducing the risk from prolonged systemic corticosteroids, orBec® is an attractive therapy in the treatment of gastrointestinal GVHD. Topical corticosteroids have been effectively used for over 25 years for inflammatory diseases of the gastrointestinal tract (ulcerative colitis, Crohn's disease, lymphocytic gastroenteritis, eosinophilic gastroenteritis) as both oral and enema formulations, with minimal complications.

12.3 Pharmacokinetics

BDP is rapidly hydrolyzed via esterase enzymes in intestinal mucosa and in the liver to an active metabolite beclomethasone-17-monopropionate (B-17-MP) which has high anti-inflammatory activity.

Systemic Absorption and Distribution: After oral administration of BDP, there are no measurable blood levels of BDP. The mean peak plasma concentration of B-17-MP following oral administration of 6x1mg IR tablets to healthy volunteers was 2,589 pg/mL at 0.13 hrs and 1,945 pg/mL at 1.2 hours following oral administration of 6x1 mg EC tablets. This compares to peak plasma concentrations following 6 mg liquid suspension of BDP administered to the same volunteers, where maximal concentration of 17-BMP was 3,373 pg/mL at 0.4 hrs. It was not possible to perform an absolute plasma bioavailability experiment, however the mean absolute bioavailability of BDP metabolites following ingestion of a liquid suspension of BDP is reported in the literature as 41%.

In vitro binding of BDP to human plasma proteins is 87%.

Metabolism and Elimination: BDP is rapidly hydrolyzed to the main product of metabolism, beclomethasone 17-monopropionate (B-17-MP) in intestinal mucosa and the liver prior to entering the systemic circulation. Minor inactive metabolites, beclomethasone-21-monopropionate (21-BMP) and beclomethasone (BOH), are also formed, but these contribute little to systemic exposure. BDP is not found in plasma after oral administration of BDP.

The mean elimination half-life of orally administered BDP, as measured by 17-BMP, is approximately 10 hours. BDP and its metabolites are predominantly excreted in the feces, with much less excreted in the urine.

12.4 Formulation

Gastrointestinal GVHD may involve the entire gastrointestinal tract. The mucosal surfaces of the stomach, small intestine and colon are the primary targets for drug activity. The predominant activity of BDP and B-17-MP is believed to be locally at the cells within the gastrointestinal tract mucosa, including both cellular and innate immune pathways.

orBec® is formulated for oral administration as a single drug product consisting of two types of tablets. One type is an immediate release (IR) tablet and the other an enteric coated (EC) tablet. Each type of tablet contains 1 mg of BDP. The only formulation difference between the two tablet types is that one has an enteric coating and the other is uncoated.

The IR and EC formulations are intended to deliver BDP to the mucosa more uniformly throughout the gastrointestinal tract when both types of tablets are administered in combination. The IR tablet is intended to release BDP in the proximal portions of the gastrointestinal tract and the EC tablet is intended to release BDP in the more distal portions of the gastrointestinal tract.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenicity of BDP was evaluated in rats which were exposed for a total of 95 weeks, 13 weeks at inhalation doses up to 0.4 mg/kg/day and the remaining 82 weeks at combined oral and inhalation doses up to 2.4 mg/kg/day. There was no evidence of carcinogenicity in this study at the highest dose, which is at doses up to 3 times greater than the recommended daily oral adult dose on a mg/m² basis.

BDP did not induce gene mutation in the bacterial cells or mammalian Chinese Hamster ovary (CHO) cells *in vitro*. No significant clastogenic effect was seen in cultured CHO cells *in vitro* or in the mouse micronucleus test *in vivo*.

In rats, BDP caused decreased conception rates at an oral dose of 16 mg/kg/day (approximately 19 times the maximum recommended daily oral dose in adults on a mg/m² basis). Impairment of fertility, as evidence by inhibition of the estrous cycle in dogs, was observed following treatment by the oral route at a dose approximately 2 times the recommended daily oral dose in adults on a mg/m² basis.

14 CLINICAL STUDIES

During the development program for orBec®, a total of 245 patients with established gastrointestinal GVHD who previously underwent allogeneic hematopoietic cell transplantation for a variety of hematological disorders were treated across 4 studies. These studies included an uncontrolled phase 1 study, a compassionate use study in patients with contraindications to high-dose corticosteroid therapy, a phase 2 randomized, double-blind, placebo-controlled study, and the phase 3 pivotal study. In these trials, a total of 96 subjects were assigned to placebo, and 151 were assigned to receive treatment with orBec®.

The safety and efficacy of orBec® were evaluated in the latter two randomized, placebo-controlled trials. In a phase 2 trial, 60 patients with gastrointestinal GVHD were studied, with 31 subjects randomized to orBec® and 29 to placebo, each for 30 days. In the pivotal phase 3, multicenter trial, 129 subjects with gastrointestinal GVHD disease were enrolled in a randomized, placebo-controlled, double-blind study with a 50-day treatment period. The subjects in the pivotal trial ranged in age from 6 to 70 years (mean 45), 60% were male and 85% were white. Of the 62 subjects randomized to receive orBec®, 5 (8%) were >65 years of age.

The primary objective of the pivotal trial was to compare the efficacy of an oral orBec® regimen (1 mg/kg/day prednisone for 10 days plus 2 mg orBec® q.i.d. for 50 days) with the efficacy of standard of care (1 mg/kg/day of oral prednisone administered for 10 days plus matching placebo tablets for 50 days) in patients with Grade II GVHD with gastrointestinal symptoms. The primary endpoint of this study was development of GVHD treatment failure. Treatment failure is defined as the requirement for additional corticosteroids over the doses prescribed by the protocol, or the addition of another immunosuppressive in response to uncontrolled GVHD during the 50-day treatment period. Based on intent-to-treat analysis, the risk of treatment failure during this period was reduced by 37% for subjects randomized to orBec® compared to placebo, however, this decrease did not achieve statistical significance (p=0.1177). Exploratory analysis demonstrates the effect of orBec® therapy was more evident in subjects who were eligible to undergo rapid taper of prednisone at the conclusion of the 10-day induction period. At Study Day 10, prednisone was tapered while continuing study drug; the subsequent risk of GVHD-treatment failure was significantly reduced for the orBec® group at Study Day 50 (hazard ratio 0.39, p=0.009) and at 30 days after discontinuation of study drug (HR 0.37, p=0.0012).

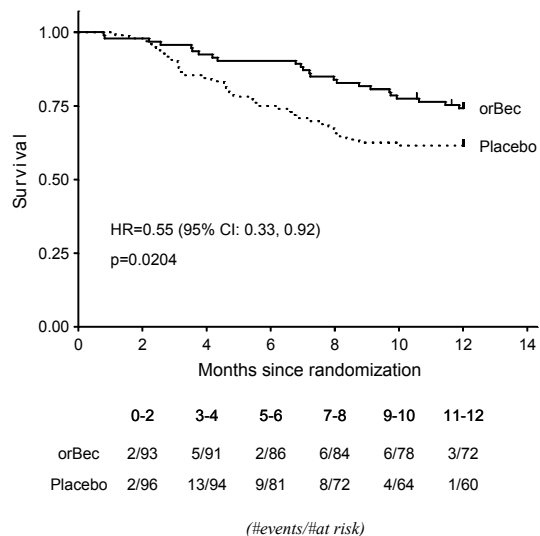
By day-200 post-transplant, 5 patients randomized to orBec® had died, compared to 16 deaths on placebo (p=0.0112). The hazard of day-200 mortality was significantly less in the orBec® group compared to placebo (HR 0.33, p=0.0294), and this difference held after adjustments for demographic-, disease-, and transplant-related factors. In 47 recipients of unrelated and HLA-mismatched stem cells, mortality at day-200 was reduced by 91% in the orBec® group, compared to placebo (HR 0.09, p=0.0217). After one year from the date of randomization, 18 of the 62 (29%) subjects randomized to receive orBec® had died, versus 28 of the 67 (48%) subjects randomized to placebo. The risk of mortality during this one-year period was 46% lower for subjects randomized to orBec® (hazard ratio 0.54, 95% CI: 0.30, 0.99; p=0.0431). Leading causes of death were relapse of the underlying malignancy and infection, both of which were seen more frequently in placebo treated subjects.

Analysis of survival in the 60-patient phase 2 randomized trial showed a similar improvement in survival at transplant day 200 and at one year after randomization. By transplant day-200, three subjects (10%) who had been randomized to orBec® had died, compared to 6 deaths (21%) among subjects who had been randomized to placebo, leading to a reduced hazard of day-200 mortality (hazard ratio 0.47, 95% CI: 0.12-1.87, p=0.28). By one year after randomization, 9 of 29 subjects in the placebo group and 6 of 31 subjects in the orBec® group had died (adjusted hazard ratio 0.55, 95% CI: 0.20-1.56, p=0.2559, stratified log-rank test). Leading causes of death were relapse of the underlying malignancy and infection.

For both studies combined, the estimated survival rates one-year after randomization were 0.74 (95% CI: 0.68, 0.81) and 0.61 (95% CI: 0.55, 0.67) for the orBec® and placebo groups, respectively. As

shown in Figure 2, the overall risk of mortality during this one-year period was 45% lower for subjects randomized to orBec® compared to placebo (hazard ratio 0.55, p=0.0204 by the stratified log-rank test).

Figure 2. Survival at one year post-randomization for Protocols 875 and ENT 00-02 combined (intent-to-treat population)



To summarize the integrated survival data from the two randomized, placebo-controlled trials:

- orBec® was administered at a fixed dose of 8 mg per day for up to 30 and 50 days in two randomized, double-blind, placebo-controlled studies.
- The survival rate at Day 200 post-transplant was higher for subjects randomized to orBec® treatment compared to placebo. The odds of mortality by Day 200 were 70% lower for orBec® relative to placebo (p=0.0054*). Infection and relapse of the underlying malignancy were the most frequently reported proximate causes of death.
- The survival rate at one year from the date of randomization was higher for subjects in the orBec® group compared to placebo. The risk of mortality was 45% lower for orBec® relative to placebo (p=0.0204*).
- Overall survival after randomization was longer for subjects randomized to orBec® treatment compared to placebo. After approximately 3.5 years of median follow-up, the risk of mortality was 37% lower for orBec® relative to placebo (p=0.0323*). Median survival after randomization was 3.8 years for placebo and was not yet reached for orBec®.

* P values are not adjusted for multiplicity.

16 HOW SUPPLIED/STORAGE AND HANDLING

orBec® is supplied as a unit of use package NDC 25232-000-00, containing 1 bottle of 200 IR tablets NDC 25232-000-01, and 1 bottle of EC tablets NDC 25232-000-02.

IR (immediate release) tablets are white to off white rectangular tablets debossed on one face with "IR" and on the other with "BDP", each containing 1 mg BDP.

EC (enteric coated) tablets are white to off white oval enteric coated tablets imprinted on one face with "EC" using black ink, each containing 1 mg BDP.

Storage

Store at 25°C (77°F); excursions permitted to 15 - 30°C (59 - 86°F) (see USP controlled room temperature). Store in a dry place.

Keep container tightly closed.

17 PATIENT COUNSELING INFORMATION

17.1. Importance of Monitoring

All patients who have received a hematopoietic cell transplant and subsequently developed graft-vs.-host disease must be closely monitored by physician and nurse examination, blood tests, and Xrays. There are substantial risks of infection, including fatal infection, in patients with GVHD, and there is a risk that GVHD will worsen. Patients who are treated with corticosteroid medications, including orBec®, are at risk for developing adrenal insufficiency as a result of suppression of the hypothalamic-pituitary-adrenal axis.

17.2. Infection

Patients should be told that the risk of infection from the transplant process, GVHD, and GVHD treatment is very high. Patients should be told to inform physicians and nurses about any new signs and symptoms that could be caused by an infection. Patients should be told that blood tests looking for incipient infections are important.

17.3. GVHD

Patients should be informed that severe GVHD is a potentially fatal disease, and thus, any worsening of skin rash, gastrointestinal symptoms, and development of jaundice must be reported immediately. It is useful to explain to patients that the dose schedule for orBec, where gastric release and enteric coated tablets are taken in combination four times daily, should be followed closely to achieve maximal benefit.

17.4. Adrenal insufficiency

Patients should be told that prolonged exposure to corticosteroid medications, including prednisone, prednisolone, and oral beclomethasone dipropionate (orBec®) may lead to suppression of the adrenal axis and may result in clinical adrenal insufficiency. Patients should be advised that blood tests for clinical adrenal insufficiency may be needed.

Manufactured by:

Pharmaceuticals International, Inc. (PII), Hunt Valley, MD 21031

Manufactured for:

Dor BioPharma, Inc., Miami, FL 33131

