CYTOMID Tablets (Flutamide)

Black Box Warning: Hepatic Injury

There have been postmarketing reports of hospitalization and rarely death due to liver failure in patients taking flutamide. Evidence of hepatic injury included elevated serum transaminase levels, jaundice, hepatic encephalopathy and death related to acute hepatic failure. The hepatic injury was reversible after discontinuation of therapy in some patients. Approximately half of the reported cases occurred within the initial 3 months of treatment with flutamide. Serum transaminase levels should be measured prior to starting treatment with flutamide. Flutamide is not recommended in patients whose ALT values exceed twice the upper limit of normal. Serum transaminase levels should then be measured monthly for the first 4 months of therapy, and periodically thereafter. Liver function tests also should be obtained at the first signs and symptoms suggestive of liver dysfunction, e.g., nausea, vomiting, abdominal pain, fatigue, anorexia, 'flu-like' symptoms, hyperbilirubinuria, jaundice or right upper quadrant tenderness. If at any time, a patient has jaundice, or their ALT rises above 2 times the upper limit of normal, flutamide should be immediately discontinued with close follow-up of liver function tests until resolution.

Composition

Each uncoated tablet contains:
Flutamide......... 250 mg

Dosage Form

Oral tablet

Pharmacology

Mechanism of action
Flutamide, an acetanilide is a nonsteroidal, orally active antiandrogen. It exerts its antiandrogenic action by inhibiting androgen uptake and/or by inhibiting nuclear binding of androgen in target tissues or both. When flutamide is given in combination with surgical or medical castration, suppression of both testicular and adrenal androgen activity is achieved. Elevations of plasma testosterone and estradiol levels have been noted following flutamide administration.

Absorption: Flutamide is rapidly and completely absorbed. Following a single 250 mg oral dose to normal adult volunteers, the biologically active alpha-hydroxylated metabolite reaches maximum plasma concentrations in about 2 hours, indicating that it is rapidly formed from flutamide. Food has no effect on the bioavailability of flutamide.

Distribution: Following a single 250 mg oral dose to normal adult volunteers, low plasma concentrations of flutamide
were detected. The plasma half-life for the alpha-hydroxylated metabolite of flutamide is approximately 6 hours. Flutamide, in vivo, at steady-state plasma concentrations of 24 to 78 ng/mL is 94% to 96% bound to plasma proteins. The active metabolite of flutamide, in vivo, at steady-state plasma concentrations of 1556 to 2284 ng/mL is 92% to 94% bound to plasma proteins.

Metabolism: The composition of plasma radioactivity, following a single 200 mg oral dose of tritium-labeled flutamide to normal adult volunteers, showed that flutamide is rapidly and extensively metabolized, with flutamide comprising only 2.5% of plasma radioactivity 1 hour after administration. At least six metabolites have been identified in plasma. The major plasma metabolite is a biologically active alpha-hydroxylated derivative which accounts for 23% of the plasma tritium 1 hour after drug administration. The major urinary metabolite is 2-amino-5-nitro-4-(trifluoromethyl) phenol. Excretion: Flutamide and its metabolites are excreted mainly in the urine with only 4.2% of a single dose excreted in the feces over 72 hours.

Pharmacokinetics in special populations

Geriatric: Following multiple oral dosing of 250 mg t.i.d. in normal geriatric volunteers, flutamide and its active metabolite approached steady-state plasma levels (based on pharmacokinetic simulations) after the fourth flutamide dose. The half-life of the active metabolite in geriatric volunteers after a single flutamide dose is about 8 hours and at steady state in 9.6 hours.

Race: There are no known alterations in flutamide absorption, distribution, metabolism, or excretion due to race.

Renal Impairment: Following a single 250 mg dose of flutamide administered to subjects with chronic renal insufficiency, there appeared to be no correlation between creatinine clearance and either C_max or AUC of flutamide. Renal impairment did not have an effect on the C_max or AUC of the biologically active alpha-hydroxylated metabolite of flutamide. In subjects with creatinine clearance of

Hepatic Impairment: No information on the pharmacokinetics of flutamide in hepatic impairment is available

Indications

- Stage B2-C Prostatic Carcinoma
  Treatment with flutamide capsules and the goserelin acetate implant should start 8 weeks prior to initiating radiation therapy and continue during radiation therapy.

- Stage D2 Metastatic Carcinoma
  To achieve benefit from treatment, flutamide capsules should be initiated with the LHRH-agonist and continued until progression.

Dosage And Administration

The recommended dosage is 2 capsules 3 times a day at 8-hour intervals for a total daily dose of 750 mg.

Contraindications

- Flutamide capsules are contraindicated in patients who are hypersensitive to flutamide or any component of this preparation.
- Flutamide capsules are contraindicated in patients with severe hepatic impairment (baseline hepatic enzymes should be evaluated prior to treatment).

Warnings And Precautions
In clinical trials, gynaecomastia occurred in 9% of patients receiving flutamide together with medical castration.

**Drug Interactions**

Increases in prothrombin time have been noted in patients receiving long-term warfarin therapy after flutamide was initiated. Therefore close monitoring of prothrombin time is recommended and adjustment of the anticoagulant dose may be necessary when flutamide capsules are administered concomitantly with warfarin.

**Hepatic Injury**

There have been postmarketing reports of hospitalization and rarely death due to liver failure in patients taking flutamide. Evidence of hepatic injury included elevated serum transaminase levels, jaundice, hepatic encephalopathy and death related to acute hepatic failure. The hepatic injury was reversible after discontinuation of therapy in some patients. Approximately half of the reported cases occurred within the initial 3 months of treatment with flutamide. Serum transaminase levels should be measured prior to starting treatment with flutamide. Flutamide is not recommended in patients whose ALT values exceed twice the upper limit of normal. Serum transaminase levels should then be measured monthly for the first 4 months of therapy, and periodically thereafter. Liver function tests also should be obtained at the first signs and symptoms suggestive of liver dysfunction, e.g., nausea, vomiting, abdominal pain, fatigue, anorexia, 'flu-like' symptoms, hyperbilirubinuria, jaundice or right upper quadrant tenderness. If at any time, a patient has jaundice, or their ALT rises above 2 times the upper limit of normal, flutamide should be immediately discontinued with close follow-up of liver function tests until resolution.

**Laboratory Tests**

Regular assessment of serum Prostate Specific Antigen (PSA) may be helpful in monitoring the patient's response. If PSA levels rise significantly and consistently during flutamide therapy the patient should be evaluated for clinical progression. For patients who have objective progression of disease together with an elevated PSA, a treatment period free of antiandrogen while continuing the LHRH analogue may be considered.

**Aniline Toxicity**

One metabolite of flutamide is 4-nitro-3-fluoromethylaniline. Several toxicities consistent with aniline exposure, including methemoglobinemia, hemolytic anemia and cholestatic jaundice have been observed in both animals and humans after flutamide administration. In patients susceptible to aniline toxicity (e.g., persons with glucose-6-phosphate dehydrogenase deficiency, hemoglobin M disease and smokers), monitoring of methemoglobin levels should be considered.

**Information for Patients**

Patients should be informed that flutamide capsules and the drug used for medical castration should be administered concomitantly, and that they should not interrupt their dosing or stop taking these medications without consulting their physician.

**Renal Impairment**

Following a single 250 mg dose of flutamide administered to subjects with chronic renal insufficiency, there appeared to be no correlation between creatinine clearance and either $C_{\text{max}}$ or AUC of flutamide. Dose adjustment in patients with chronic renal insufficiency is not warranted.
No information on flutamide use in patients with hepatic impairment is available.

### Pregnancy

**Pregnancy Category D**

Flutamide capsules are for use only in men. This product has no indication for women, and should not be used in this population, particularly for non-serious or non-life-threatening conditions.

There was decreased 24-hour survival in the offspring of pregnant rats treated with flutamide at doses of 30, 100, or 200 mg/kg/day (approximately 3, 9, and 19 times the human dose). A slight increase in minor variations in the development of the sternebrae and vertebrae was seen in fetuses of rats treated with two higher doses. Feminization of the male rats also occurred at the two higher dose levels. There was a decreased survival rate in the offspring of rabbits receiving the highest dose (15 mg/kg/day, equal to 1.4 times the human dose).

### Lactation

Flutamide capsules are for use only in men. This product has no indication for women, and should not be used in this population, particularly for non-serious or non-life-threatening conditions.

### Undesirable Effects

#### Stage B2-C Prostatic Carcinoma

Treatment with flutamide capsules and the goserelin acetate implant did not add substantially to the toxicity of radiation treatment alone. The following adverse experiences were reported during a multicenter clinical trial comparing flutamide + goserelin acetate implant + radiation versus radiation alone. The most frequently reported (greater than 5%) adverse experiences are listed below.

Additional adverse event data were collected for the combination therapy with radiation group over both the hormonal treatment and hormonal treatment plus radiation phases of the study. Adverse experiences occurring in more than 5% of patients in this group, over both parts of the study, were hot flashes (46%), diarrhea (40%), nausea (9%), and skin rash (8%).
Adverse Events During Acute Radiation Therapy (within first 90 days of radiation therapy)

<table>
<thead>
<tr>
<th></th>
<th>(n = 231)</th>
<th>(n = 235)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goserelin Acetate Implant + Flutamide + Radiation</td>
<td>% All</td>
<td>Radiation Only % All</td>
</tr>
<tr>
<td>Rectum/Large Bowel</td>
<td>80</td>
<td>76</td>
</tr>
<tr>
<td>Bladder</td>
<td>58</td>
<td>60</td>
</tr>
<tr>
<td>Skin</td>
<td>37</td>
<td>37</td>
</tr>
</tbody>
</table>

Adverse Events During Late Radiation Phase (after 90 days of radiation therapy)

<table>
<thead>
<tr>
<th></th>
<th>(n = 231)</th>
<th>(n = 235)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goserelin Acetate Implant + Flutamide + Radiation</td>
<td>% All</td>
<td>Radiation Only % All</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36</td>
<td>40</td>
</tr>
<tr>
<td>Cystitis</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Rectal Bleeding</td>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td>Proctitis</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Hematuria</td>
<td>7</td>
<td>12</td>
</tr>
</tbody>
</table>

Stage D2 Metastatic Carcinoma

The following adverse experiences were reported during a multicenter clinical trial comparing flutamide + LHRH agonist versus placebo + LHRH agonist. The most frequently reported (greater than 5%) adverse experiences during treatment with flutamide capsules in combination with an LHRH agonist are listed in the table below. For comparison, adverse experiences seen with an LHRH
agonist and placebo are also listed in the following table.

<table>
<thead>
<tr>
<th></th>
<th>(n=294) Flutamide + LHRH agonist % All</th>
<th>(n=285) Placebo + LHRH agonist % All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot Flashes</td>
<td>61</td>
<td>57</td>
</tr>
<tr>
<td>Loss of Libido</td>
<td>36</td>
<td>31</td>
</tr>
<tr>
<td>Impotence</td>
<td>33</td>
<td>29</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Other GI</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

As shown in the table, for both treatment groups, the most frequently occurring adverse experiences (hot flashes, impotence, loss of libido) were those known to be associated with low serum androgen levels and known to occur with LHRH agonists alone.

The only notable difference was the higher incidence of diarrhea in the flutamide + LHRH agonist group (12%), which was severe in 5% as opposed to the placebo + LHRH agonist (4%), which was severe in less than 1%.

In addition, the following adverse reactions were reported during treatment with flutamide + LHRH agonist.

- **Cardiovascular System:** hypertension in 1% of patients.
- **Central Nervous System:** CNS (drowsiness/confusion/depression/anxiety/nervousness) reactions occurred in 1% of patients.
- **Gastrointestinal System:** anorexia 4%, and other GI disorders occurred in 6% of patients.
- **Hematopoietic System:** anemia occurred in 6%, leukopenia in 3%, and thrombocytopenia in 1% of patients.
- **Liver and Biliary System:** hepatitis and jaundice in less than 1% of patients.
- **Skin:** irritation at the injection site and rash occurred in 3% of patients.
- **Other:** edema occurred in 4%, genitourinary and neuromuscular symptoms in 2%, and pulmonary symptoms in less than 1% of patients. In addition, the following spontaneous adverse experiences have been reported during the marketing of flutamide: hemolytic anemia, macrocytic anemia, methemoglobinemia, sulfhemoglobinemia, photosensitivity reactions (including erythema, ulceration, bullous eruptions, and epidermal necrolysis), and urine discoloration. The urine was noted to change to an amber or yellow-green appearance which can be attributed to the flutamide and/or its metabolites. Also reported were cholestatic jaundice, hepatic encephalopathy, and hepatic necrosis. The hepatic conditions were often reversible after discontinuing therapy; however, there have been reports of death following severe hepatic injury associated with use of flutamide.
- **Malignant breast neoplasms** have occurred rarely in male patients being treated with flutamide.
- **Abnormal Laboratory Test Values:** Laboratory abnormalities including elevated SGOT, SGPT, bilirubin values, SGGT, BUN, and serum creatinine have been reported.

**Overdosage**
Clinical trials have been conducted with flutamide in doses up to 1500 mg per day for periods up to 36 weeks with no serious adverse effects reported. Those adverse reactions reported included gynecomastia, breast tenderness, and some increases in SGOT. The single dose of flutamide ordinarily associated with symptoms of overdose or considered to be life-threatening has not been established.

Flutamide is highly protein bound and is not cleared by hemodialysis. As in the management of overdosage with any drug, it should be borne in mind that multiple agents may have been taken. If vomiting does not occur spontaneously, it should be induced if the patient is alert. General supportive care, including frequent monitoring of the vital signs and close observation of the patient, is indicated.

### Storage And Handling Instructions

Store below 25-C.

### Packaging Information

CYTOMID: Strip of 10 tablets  
*Last updated: December 2013*  
*Last reviewed: December 2013*

### CYTOMID Tablets

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