- Sustained release preparation for the treatment of prostatic hypertrophy -

**PROSTAL®-L TABLETS 50mg**

*<Chlormadinone Acetate>*

prescription-only drug

Caution: Use only pursuant to the prescription or direction of a physician, etc.

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### STORAGE

The product should be stored at room temperature.

### APPROVAL NO.

22100AMX00929

### DATE OF LISTING IN THE NHI REIMBURSEMENT PRICE

September 2009

### DATE OF INITIAL MARKETING IN JAPAN

August 1990

### DATE OF LATEST REEXAMINATION

March 1998

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### CONTRAINDICATIONS (PROSTAL-L TABLETS are contraindicated in the following patients.)

Patients with severe hepatic impairment or diseases

[Symptoms may be aggravated due to decreased metabolic functions and increased load to the liver.]

### DESCRIPTION

1. **Composition**

   **PROSTAL-L TABLETS 50mg:**
   
   Each tablet contains 50 mg of chlormadinone acetate (The Japanese Pharmacopoeia).

2. **Product description**

   **Brand name**
   
   PROSTAL-L TABLETS 50mg

   **Dosage form**
   
   Light yellow film-coated sustained release tablet

   **Inactive ingredients**
   
   Carnauba wax, glycerin fatty acid ester, closoxymellose sodium, titanium oxide, magnesium stearate, hypromellose pthalate, methacrylic acid copolymer-S, magnesium aluminometasilicate

   **Diameter** : ca. 9.2 mm
   
   **Thickness** : ca. 4.6 mm
   
   **Weight** : 283 mg

   **Identification code**
   
   TZ326

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### INDICATIONS

Prostatic hypertrophy.

### DOSAGE AND ADMINISTRATION

Usually for adults, one tablet (50 mg of chlormadinone acetate) is orally administered once a day after meals.

### PRECAUTIONS

1. **Careful Administration (PROSTAL-L TABLETS should be administered with care in the following patients.)**

   (1) Patients with cardiac or renal disorders or their history
   
   [Due to the retention of sodium or body fluids, the symptoms may be aggravated.]

   (2) Patients with diabetes mellitus
   
   [Decrease in glucose tolerance may occur.]

2. **Important Precautions**

   (1) Liver function tests should be conducted at least once a month until three months after start of administration, and afterwards periodically, because death cases by a serious liver dysfunction such as the fulminant hepatitis have been reported.

   (2) Note that the treatment of prostatic hypertrophy with the drug is not a radical treatment. If the treatment fails to exert an expected effect, take appropriate measures such as surgery or any other treatment.

   (3) One course of the administration is 16 weeks, in principle. In case an expected effect is not exerted, do not continue the administration carelessly.

   (4) If impotence or other undesirable symptoms appear, the administration should be suspended or other treatment should be taken, if necessary, in consideration of therapeutic benefit.

3. **Adverse reactions**

   Of the 3,607 patients with prostatic hypertrophy investigated in the clinical trials and at post-marketing survey, 199 patients (5.52%) of adverse reactions, including abnormal laboratory values, were reported. Chief adverse reactions were impotence (2.33%), decreased libido (0.69%), anaemia (0.47%), etc. (as of the end of reexamination).
(1) Clinically significant adverse reactions

1) Congestive heart failure (incidence unknown) :
   Congestive heart failure may occur. In such cases, take
   appropriate measures such as discontinuation of the
   treatment with the drug.

2) Thrombosis (less than 0.1%) : Thrombosis (brain,
   heart, lung, extremities, etc.) may occur. In case of
   abnormalities, discontinue the treatment with the drug
   and take appropriate measures.

3) Fulminant hepatitis (incidence unknown), hepatic
   function disorder or jaundice (less than 0.1%,
   respectively) : Liver function tests should be
   conducted at least once a month until three months
   after start of administration, and afterwards
   periodically, because death cases by fulminant
   hepatitis, hepatic disorder or jaundice after 1-2 months
   from start of administration have been reported. In
   case of abnormalities such as nausea and vomiting,
   anorexia, general malaise, discontinue the treatment
   with the drug and take appropriate measures.

4) Diabetes mellitus, aggravation of diabetes mellitus
   or hyperglycaemia (incidence unknown) : Diabetes
   mellitus, aggravation of diabetes mellitus or
   hyperglycaemia may occur, and serious cases with
   coma and ketoacidosis have been reported. Careful
   observation such as observation of blood sugar level or
   urine sugar should be made. In case of abnormalities,
   take appropriate measures such as discontinuation of
   the treatment with the drug.

(2) Other adverse reactions

<table>
<thead>
<tr>
<th>Incidence</th>
<th>5%&gt; ≥0.1%</th>
<th>&lt;0.1%</th>
<th>Incidence unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reproductive</td>
<td>Impotence, decreased libido, etc.</td>
<td></td>
<td></td>
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<tr>
<td>Hypersensitivity</td>
<td>Pruritus, Rash, etc.</td>
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<td></td>
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<tr>
<td>Hepatic</td>
<td>Abnormal hepatic function, etc.</td>
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<tr>
<td>Renal</td>
<td>Increased BUN and creatinine, etc.</td>
<td></td>
<td></td>
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<tr>
<td>Electrolytes</td>
<td>Weight increase, etc.</td>
<td></td>
<td>Edema, etc.</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Heart pounding, breath shortness, etc.</td>
<td></td>
<td>Palpitation, distressed feeling of chest, etc.</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Anemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Anorexia, stomach discomfort, thirst, etc.</td>
<td></td>
<td>Nausea, vomiting, diarrhea, constipation, abdominal pain, etc.</td>
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<tr>
<td>Psychoneurologic</td>
<td>Headache, drowsiness, etc.</td>
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<td></td>
</tr>
<tr>
<td>Urinary</td>
<td>Pollakiuria, etc.</td>
<td></td>
<td>Urethral discomfort, lower abdominal pain, etc.</td>
</tr>
<tr>
<td>Lipid metabolic</td>
<td>Increased triglyceride</td>
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<tr>
<td>Endocrine</td>
<td>Gynecomastia</td>
<td></td>
<td>Decreased serum FSH, LH and testosterone, increased prolactin</td>
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<tr>
<td>Skin</td>
<td>Alopecia</td>
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</tbody>
</table>

4. Use in the Elderly
To elderly patients, administer the drug with taking such measures as the consideration of the dosage interval.
[Since the elderly may often have a reduced physiological function, high blood concentration may persist.]

5. Precautions Concerning Use at dispensing drugs
For drugs that are dispensed in a press-through package
(PTP), instruct the patient to remove the drug from the
package prior to use. (It has been reported that, if the PTP
sheet is swallowed, the sharp corners of the sheet may
puncture the esophageal mucosa, resulting in severe
complications such as mediastinitis.)

6. Other Precautions
Aspermatogenesis in rats, rabbits and dogs has been reported. Atrophy of adrenal cortex has been reported in rats and dogs, but not reported in guinea pigs.

PHARMACOKINETICS
When one tablet of PROSTAL-L TABLETS was orally administered to healthy male adults at the fasting state, the plasma concentration reached the maximum level at 5.1 hours (Tmax) after the administration with a half-life of 10.2 hours (T1/2), showing the sustained release pattern of plasma concentration compared with ordinary chlormadinone acetate tablets.

<table>
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<tr>
<th>Incidence unknown</th>
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</table>

4) Patients should be observed carefully. In such case, appropriate measures, such as discontinuation of the treatment with the drug, etc., should be taken.

CLINICAL STUDIES
1. In a double-blind clinical trial in which the patients with prostatic hypertrophy who claimed urinary dysfunction received this drug one tablet once daily and ordinary chlormadinone acetate 25 mg tablets (as a reference) one tablet twice daily for 16 weeks, the efficacy rates of the drug and 25 mg tablets were as follows:

<table>
<thead>
<tr>
<th>Others</th>
<th>Slight fever</th>
<th>Malaise, diaphoresis</th>
<th>Obesity</th>
</tr>
</thead>
</table>

   11) In such cases, the treatment with the drug should be discontinued.
   12) Patients should be observed carefully such as taking care of hepatic functions. In the event of abnormality, appropriate measures, such as discontinuation of the treatment with the drug, etc., should be taken.
   13) In such cases, appropriate measures, such as discontinuation of the treatment with the drug, etc., should be taken.
   14) Patients should be observed carefully. In such case, appropriate measures, such as discontinuation of the treatment with the drug, etc., should be taken.
2. The efficacy rate in the open labeled clinical trials in which the patients with prostatic hypertrophy who claimed urinary dysfunction received this drug one tablet once daily for 12 to 16 weeks was 65.8% (50/76). 4,6

PHARMACOLOGY

1. Chlormadinone acetate, with its anti-androgenic action (direct inhibitory effect on prostate), exerts an inhibitory effect on hypertrophic prostate, atrophic effects on prostate. (1) It inhibits hypertrophy of prostate by antagonizing exogenous androgens. (Castrated male Wistar rats7) (2) It atrophies prostate by antagonizing endogenous androgens. (Male Wistar rats7)

2. Chlormadinone acetate exerts a direct inhibitory effect on prostate through the following mechanisms of action: (1) It is selectively taken into prostate and exerts an inhibitory effect in prostatic cells. (Male Wistar rats8) (2) It inhibits selective uptake of testosterone into prostate. (Castrated male Wistar rats8) (3) It inhibits binding of 5α-dihydrotestosterone to receptors. (Castrated male SD rats; ventral prostate cells8,9)

PHYSICOCHEMISTRY

Nonproprietary name: Chlormadinone Acetate [JAN]
Chemical name: 6-Chloro-3,20-dioxopregna-4,6-dien-17-yl acetate
Molecular formula: C23H29ClO4
Structural formula:

Molecular weight: 404.93
Melting point: 211-215°C
Description: Chlormadinone acetate occurs as white to light yellow crystals or crystalline powder. It is odorless. It is freely soluble in chloroform, soluble in acetonitrile, slightly soluble in ethanol(95) and in diethylether, and practically insoluble in water.

PACKAGING

PROSTAL-L TABLETS 50mg:
- Boxes of 100 tablets (10 tab. × 10)
- Boxes of 140 tablets (14 tab. × 10)
- Boxes of 500 tablets (10 tab. × 50)
- Bottles of 500 tablets
- Boxes of 700 tablets (14 tab. × 50)

REFERENCES


REQUEST FOR LITERATURE AND INQUIRIES OF PRODUCT INFORMATION SHOULD BE MADE TO:
Drug Information Unit
ASKA Pharmaceutical Co., Ltd.
5-1, Shibaura 2-chome, Minato-ku, Tokyo, 108-8532 Japan
TEL 0120-848-339  03-5484-8339
FAX 03-5484-8358

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1-1, Doshomachi 4-chome, Chuo-ku, Osaka, Japan

BRAND NAMES IN OTHER COUNTRIES
PROSTAL-L (Korea)