- AGENT FOR IMPROVEMENT IN LIPID METABOLISM AND PERIPHERAL CIRCULATION -

CHOLEXAMIN® Tablets 200 mg

< JP Nicomol tablet >

<table>
<thead>
<tr>
<th>Storage</th>
<th>This product should be stored at room temperature.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expiration date</td>
<td>This product should be used before the expiration date indicated on the outer cases and containers.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Approval No.</th>
<th>21900AMX00774000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of listing in the NHI reimbursement price</td>
<td>June 2007</td>
</tr>
<tr>
<td>Date of initial marketing in Japan</td>
<td>June 2007</td>
</tr>
<tr>
<td>Date of added indications</td>
<td>September 1974</td>
</tr>
<tr>
<td>Date of latest reevaluation</td>
<td>June 1992</td>
</tr>
</tbody>
</table>

CONTRAINDICATIONS (This product is contraindicated in the following patients.)

Patients with severe hypotension or persistent hemorrhage
[Administration of this product may exacerbate hypotension and enhance hemorrhage by peripheral vasodilation.]

DESCRIPTION

<table>
<thead>
<tr>
<th>Ingredient/content per tablet</th>
<th>JP Nicomol 200 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactive ingredients</td>
<td>Lactose hydrate, crystalline cellulose, corn starch, powdered acacia, magnesium stearate</td>
</tr>
</tbody>
</table>

| Dosage form | Plain |
| Color | White |
| Appearance | 8.5 mm in diameter / 4.4 mm in thickness / About 250 mg in weight |
| Identification code | KP-160 |

INDICATIONS

Hyperlipemia
Improvement in peripheral circulatory disorder resulting from the following diseases
Chilblain, limb arterial occlusive disease (obstructive thromboarteritis and arteriosclerosis obliterans), Raynaud syndrome

DOSAGE AND ADMINISTRATION

The usual adult dosage of this product for oral use is 200 to 400 mg of Nicomol three times daily after meals.
The dosage may be adjusted according to patients’ ages and symptoms.

PRECAUTIONS

1. Careful Administration (This product should be administered with care in the following patients.)

   (1) Patients with glaucoma
   [Administration of this product may increase blood flow of the retinal vessels to elevate intraocular pressure by peripheral vasodilatation.]

   (2) Patients with hepatic dysfunction
   [Overdosage of a related drug (nicotinic acid) has been reported to induce abnormal hepatic function.]

   (3) Patients with peptic ulcer
   [Administration of a related drug (nicotinic acid) has been reported to exacerbate peptic ulcer.]

2. Drug Interactions

   (1) Precautions for coadministration (This product should be administered with care when coadministered with the following drugs.)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Signs, Symptoms and Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMG-CoA reductase inhibitors: Simvastatin, pravastatin sodium, etc.</td>
<td>Coadministration of these drugs with a related drug (nicotinic acid) has been reported to frequently induce rhabdomyolysis along with acute exacerbation of renal function characterized by myalgia, weakness, increased CK (CPK), and increases in blood and urinary myoglobin.</td>
</tr>
</tbody>
</table>

3. Adverse Reactions

This product has not been investigated (Drug-use results surveys, etc.) to determine the incidence of adverse reactions. The incidence data on this product have therefore been collected from the literature.

Out of a total of 5265 cases, 610 cases (11.6%) had adverse reactions (including laboratory test abnormalities). The most common reactions included 316 events (6.00%) of hot flushes/hot feeling, 126 (2.39%) of rash, and 108 (2.05%) of redness (the results of reevaluation).
(1) Other adverse reactions

<table>
<thead>
<tr>
<th>Category</th>
<th>5%≤</th>
<th>0.1≤ &lt;5%</th>
<th>&lt;0.1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyper-sensitivity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Note</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastro-intestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Note</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psycho-neurologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
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</tbody>
</table>

Note: When any of adverse reactions is observed, administration should be discontinued.

4. Use in the Elderly
Since elderly patients often have reduced physiological functions, careful supervision and measures such as a reduction in the dose are recommended.

5. Use during Pregnancy, Delivery or Lactation
Administration of this product to pregnant or possibly pregnant women is not recommended.
[The safety of this product for use during pregnancy has not been established.]

6. Precautions Concerning Use
(1) Precautions during administration: Since administration of this product in a fasted state increases the incidences of hot flushes and rash, administration just after meals is recommended.

(2) Precautions regarding dispensing: For the drug that is dispensed in a press-through package (PTP), patients should be instructed to remove the drug from the PTP sheet prior to use.
[It has been reported that if the PTP sheet is swallowed, its sharp corners may puncture the esophageal mucosa, resulting in serious complications such as mediastinitis.]

7. Other Precautions
It has been reported that overdosage of a related drug (nicotinic acid) induces abnormal hepatic function, and exacerbates diabetes mellitus and peptic ulcer.

PHARMACOKINETICS

1. Blood Concentrations

When Nicomol at a single dose of 400 mg was orally administered to healthy adults at 30 minutes after a meal, the pharmacokinetic parameters of free nicotinic acid are as follows:

<table>
<thead>
<tr>
<th></th>
<th>Tmax (hr)</th>
<th>Cmax (μg/mL)</th>
<th>AUC0→8 (μg·h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free nicotinic acid</td>
<td>2.2</td>
<td>0.25</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Free nicotinic acid was determined by a mass fragmentography (MF) using a gas chromatography mass spectrometry (GC/MS).

2. Metabolism and Excretion
Nicomol, an ester form of nicotinic acid, is hydrolyzed after oral administration to metabolize into nicotinic acid and 2,2,6,6-tetrais(hydroxymethyl)cyclohexanol (THC). When Nicomol at a single dose of 400 mg was orally administered to healthy adults at 30 minutes after a meal, 49% of the dose was excreted in urine as THC within 24 hours after administration.

CLINICAL STUDIES

Clinical Response
The following are the summaries of the results of the clinical studies including three double-blind comparative studies in a total of 920 cases at 37 medical institutions:

(1) Blood lipid metabolism abnormality (hyperlipidemia)
Out of cases with hypertension or arteriosclerosis in which total cholesterol in serum before administration was no less than 220 mg/dL, the rates of cases with decreases of 10% or more and 5% or more in total cholesterol were 62.6% (159/254) and 77.6% (197/254), respectively.
In addition, the usefulness of this product was confirmed in the double-blind comparative studies.

(2) Peripheral circulatory disorder
The effective rates classified into the “effective” category were 63.2% (24/38) in chilblain, 50.6% (80/158) in obstructive thromboarteritis, 61.5% (40/65) in arteriosclerosis obliterans, and 87.2% (41/47) in Raynaud syndrome. The respective rates including the “fair effective” category were 76.3% (29/38), 69.0% (109/158), 78.5% (51/65), and 87.2% (41/47).
In addition, the usefulness of this product was confirmed in the double-blind comparative studies.

PHARMACOLOGY

1. Clinical Pharmacology

(1) This product decreases total cholesterol and triglyceride in patients with hyperlipidemia.

(2) This product improves the index of arteriosclerosis by increasing HDL-cholesterol and decreasing VLDL- and LDL-cholesterols in patients with hyperlipidemia. For HDL-cholesterol, HDL2-cholesterol, which is known to have a potent anti-atherogenic action, was markedly increased.
2. Pre-clinical Pharmacology

(1) Improvement in lipid metabolism

1) Cholesterol
   • This product inhibits absorption of cholesterol from the digestive tract (mice).\(^7\)
   • This product has a choleretic action, and facilitates catabolism and excretion of cholesterol (rats).\(^8\)
   • This product decreases cholesterol in the body tissues (mice).\(^7\)

2) Triglycerides\(^9\)
   • This product inhibits absorption of triglycerides from the digestive tract (rats).
   • This product increases the level of blood lipoprotein lipase to facilitate degradation and transfer toward the tissues of triglycerides (rats).

3) Free fatty acid\(^10\)
   This product suppresses an increase in serum free fatty acid due to adrenaline (rabbits).

(2) Effect on coagulation-fibrinolysis system

1) Prostaglandins\(^11\)
   This product inhibits biosynthesis of thromboxane A\(_2\) in platelets and facilitates that of prostaglandin I\(_2\) in vascular endothelial cells to suppress platelet aggregation (\textit{in vitro}).

2) Plasmin\(^10\)
   This product has a mild plasmin-activating action to prevent thrombogenesis and coagulation (rabbits).

(3) Improvement in peripheral circulation

This product facilitates biosynthesis of prostaglandin I\(_2\) in vascular endothelial cells to relax vessels (\textit{in vitro}).\(^11\) In addition, it may facilitate vascular relaxation by increasing Ca\(^{2+}\) - and Mg\(^{2+}\)-ATPase activities in bovine aortic muscle microsomes to remove Ca\(^{2+}\) from adrenergic fibers.\(^12\)

\textbf{PHYSICOCHEMISTRY}

\begin{itemize}
  \item \textbf{Nonproprietary name:} Nicomol (JAN)
  \item \textbf{Chemical name:} (2-Hydroxycyclohexane-1,1,3,3-tetrayl) tetramethyl tetranicotinate
  \item \textbf{Molecular formula:} C\(_{34}\)H\(_{32}\)N\(_4\)O\(_9\)
  \item \textbf{Molecular formula:} C\(_{34}\)H\(_{32}\)N\(_4\)O\(_9\)
  \item \textbf{Molecular weight:} 640.64
\end{itemize}

\textbf{Structural formula:}

\begin{center}
\begin{tikzpicture}
  % Structural formula image here
\end{tikzpicture}
\end{center}

\textbf{Melting point:} 181 to 185 °C

\textbf{Description:}
Nicomol occurs as a white crystalline powder, without odor and taste. It is soluble in chloroform, and practically insoluble in water, ethanol (95), and diethyl ether. In addition, it is soluble in dilute hydrochloric acid and dilute nitric acid.

\textbf{Partition coefficient:}
Nicomol is not distributed to the water layer in chloroform-water system at pH values of 3 to 13 at 24 °C.

\textbf{PACKAGING}
100 tablets (10 tablets x 10) or 500 tablets (10 tablets x 50) in a press-through package
500 tablets in a bottle

\textbf{REFERENCES}
1) Kawahara T. et al., Pharmacokinetic study of nicomol (In-house data)
2) Nakamura H. et al., Geriatric Medicine, 18, 1141 (1980)
3) Nakamura Y. et al., Geriatric Medicine, 19, 261 (1981)
8) Irikura T. et al., Pharmacometrics, 2, 259 (1968)
10) Irikura T. et al., Pharmacometrics, 2, 237 (1968)

\textbf{REQUEST FOR LITERATURE SHOULD BE MADE TO:}
A request for in-house data mentioned in the References can also be made to the following.
Kyorin Pharmaceutical Co., Ltd. Drug Information Center
6, Kanda surugadai 4-chome, Chiyoda-ku, Tokyo 101-8311, Japan
TEL: 0120-409-341 (Toll-free)
9:00 to 17:30 (Monday through Friday exclusive of national holidays)

\textbf{Manufactured and Marketed (Imported) by:}
Kyorin Pharmaceutical Co., Ltd.
6, Kanda Surugadai 4-chome, Chiyoda-ku, Tokyo 101-8311, Japan