TONOGEN

(Hematoporphyrin Hydrochloride + B12)

SUMMARY OF PRODUCT CHARACTERISTICS

1. TRADE NAME OF THE MEDICAL PRODUCT

TONOGEN

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of diluents contains:

<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematoporphyrin Hydrochloride</td>
<td>2mg</td>
</tr>
<tr>
<td>Excipients</td>
<td></td>
</tr>
<tr>
<td>Sorbitol, liquid (non-crystallising) 70%</td>
<td>7.5g</td>
</tr>
<tr>
<td>Sodium Acetate</td>
<td>5mg</td>
</tr>
<tr>
<td>Tribasic Sodium Citrate</td>
<td>36mg</td>
</tr>
<tr>
<td>Methyl p-hydroxybenzoate</td>
<td>16mg</td>
</tr>
<tr>
<td>Raspberry Soluble Natural Aroma 1:800</td>
<td>10mg</td>
</tr>
<tr>
<td>Ethanol</td>
<td>0.5ml</td>
</tr>
<tr>
<td>Polyvinyl Pyrrolidone</td>
<td>200mg</td>
</tr>
<tr>
<td>Dehydroacetic acid (sodium salt)</td>
<td>4mg</td>
</tr>
<tr>
<td>Sodium Salt Ethylenediamine Tetraacetic Acid</td>
<td>1mg</td>
</tr>
<tr>
<td>(EDTA sodium salt)</td>
<td></td>
</tr>
<tr>
<td>Potassium Sorbate</td>
<td>20mg</td>
</tr>
<tr>
<td>Purified water</td>
<td>g. 4</td>
</tr>
</tbody>
</table>

Each cartridge-cap contains:

<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyanocobalamin (Vit.B12)</td>
<td>1mg</td>
</tr>
<tr>
<td>Excipients</td>
<td></td>
</tr>
<tr>
<td>Mannitol</td>
<td>100mg</td>
</tr>
<tr>
<td>Sucrose</td>
<td>50mg</td>
</tr>
</tbody>
</table>

3. PHARMACEUTICAL FORM

10 ml vials with cartridge-cap for oral use.
4. **CLINICAL INFORMATION**

4.1 **Therapeutic indications**
Asthenia and physical and mental depression; haematopoiesis, vitamin deficiency.

4.2 **Posology and method of administration**
Two or more vials daily according to the physicians’ prescription to be taken before the main meals.
- **Instruction for use** –
  Remove the cover and push the plunger to release the cap content into the diluent. Shake until the powder is completely dissolved.

4.3 **Contraindications**
Individual hypersensitivity reported versus one or more components.
Hematoporphyrin – At the recommended doses is contraindicated in patients affected by porphyria and photosensitivity.

4.4 **Special precautions**
No risk of abuse, dependence or other.

**KEEP OUT OF THE REACH AND SIGHT OF CHILDREN**

4.5 **Drug interactions and others**
Not reported in either the literature or clinical practice

4.6 **Use in pregnancy and lactation**
No side effects have been reported that could contraindicate the use of the product during pregnancy or lactation. In these situations, TONOGEN may be used under a physician control.

4.7 **Effects on ability to drive and use machines**
The literature and monitoring have reported no interference of TONOGEN on the ability to drive motor vehicles or operate dangerous machinery.

4.8 **Undesirable effects**
No serious side effects have been reported

4.9 **Overdosage**
Manifestations of intoxication from overdosage have not been observed in humans. In case of inadvertent ingestion of TONOGEN in greater-than-therapeutic dose levels, symptomatic and supportive treatments are recommended.

5. **PHARMACO-TOXICOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic and Pharmacokinetics properties; toxicological data**

Hematoporphyrin
It is a synthesized tetrapyrrol able to interact readily with suitable biologic substrates.
In laboratory animals the administration of hematoporphyrin stimulates food intake without leading to increase in body weight, which may be due to the simultaneous rise in motor activity.
In CDR rats hematoporphyrin improves learning ability, while in normal rats, it improves neurotor control and resistance to fatigue. Hematoporphyrin works on the CNS partly through a serotonin-like mode action. In clinical trials hematoporphyrin demonstrated antidepressive and antianemic effects by significantly improving the coenaesthesia in treated subjects. Blood and laboratory data showed a specific, stimulating effect on erythropoiesis without modifying leukocyte or platelet counts. The “in vivo” study on ferrokinetics and the “in vitro” demonstration of the rise in the synthesis of DNA and RNA, and thus of cellular maturation, strongly suggest proof of its antianemic action. Additionally, hematoporphyrin has marked antidepressive effect according to the parameters of the Hamilton Rating Scale.

**Acute toxicity**
The LD$_{50}$ in the mouse for intraperitoneal administration was over 160 mg/kg and over 270 mg/kg in the rat. The LD$_{50}$ by oral administration also at doses of 1300 mg/kg in the mouse and 3000 mg/kg in the rat could not be established.

**Subacute toxicity**
Hematoporphyrin administered by intraperitoneal route at a dose of 50 mg/kg by mouth at a dose of 600 mg/kg/per day in the rat for 14 weeks showed that the drug was well tolerated and without toxic effects.

Pharmacokinetic studies conducted on the rat and the dog with marked hematoporphyrin showed that the substance is absorbed following oral and parenteral administration. The target organs are the liver and secondarily the kidney. The substance was able to cross the blood brain barrier and to reach cerebral tissues.

Vitamin B12 (cyanocobalamin) is a precursor of the active coenzyme 5-adenosylbalamin and methylcobalamin that are indispensable for growth and cellular replication, for the normal throphism of myelin, for the synthesis of methionine and succinyl CoA. Among the manifestations that characterise vitamin B12 deficiency are a deficit in the production of erythrocytes with the appearance of megaloblastic anaemia and anatomic and functional changes in the nervous system.

6. **PHARMACEUTICAL INFORMATION**

6.1 **Incompatibility**
No incompatibility with other substances reported.

6.2 **Shelf life**
36 months

6.3 **Special precautions for storage**
The product must be stored under “normal room temperature conditions”, according to F.U.IX Ed.

6.4 **Nature and content of container**
Transparent glass vials with cartridge-cap, sealed with pull-off closure, packed in heavy, labelled carton with glued edges, package leaflet inside. Boxes of 10 vials
6.5. **Instructions for use and handling**
No particular precautions need be taken in handling the product. See method of administration.

7. **MARKETING AUTHORIZATION HOLDER**
ABC FARMACEUTICI S.P.A.
CORSO VITTORIO Emanuele II, 72
10121 TURIN

8. **MARKETING AUTHORIZATION NUMBER**

code No. 021229036

9. **DATE OF FIRST AUTHORIZATION**

04.02.1991 (with the actual formulation)
Authorization renewal and artworks revision: May 2005

10. **DATE OF REVISION OF THE TEXT** July 2005