RECOMBINANT HUMAN GROWTH HORMONE (rhGH) THERAPY: FACTS TO CONSIDER ABOUT DRY POWDER AND LIQUID FORMULATIONS

An overview of the differences between dry powder and liquid formulations and the additives, injection volume and pH of Genotropin and other currently available human recombinant growth hormone formulations.

This brochure is provided by Pfizer Endocrine Care as a service to discuss the differences in composition between dry powder and liquid formulations of human recombinant growth hormone.
An overview of the differences between dry powder and liquid formulations

The unstable nature of proteins requires that they be protected

- Proteins, such as recombinant growth hormone, are highly sensitive to their environment
  - Exposure to freezing, heat, agitation or fluorescent light can all affect the stability of rhGH
- Measures must be taken to protect proteins from undergoing detrimental changes, both in the manufacturing process and during storage

How Dry Powder and Liquid Formulations Protect rhGH

Recombinant growth hormone formulations are designed to protect the fragile growth hormone protein. There are two types of rhGH formulations: dry powder and liquid. Based on the type of formulation, the additives and quantity of additives vary. Multi-dose rhGH formulations (dry powder or liquid) may include the following types of additives to maintain the integrity of the product:

- **Buffers** maintain an optimal pH, which minimizes protein degradation
- **Bulking Agents** are used to provide bulk to formulation
- **Preservatives** are added to protect the formulation from microbial contamination
- **Stabilizers** further protect the rhGH protein
- **Surfactants** reduce clumping (aggregation) of rhGH molecules in solution
- **Tonicity adjusters** make the formulation isotonic with body fluids

How proteins are maintained in a multi-dose liquid formulation

A liquid formulation relies primarily on a balance of chemicals added to the formulation to maintain the integrity of the rhGH.

Maintaining the rhGH in a liquid has the following implications to the formulation:

- When large proteins are suspended in a liquid, the proteins tend to clump together. Therefore, an additive called a surfactant is introduced to prevent the clumping.
- When stored as a multi-dose liquid formulation, preservative must be added to protect rhGH from microbial degradation and contamination.
- When stored as part of a multi-dose liquid formulation, preservatives are part of the rhGH formulation for the entire shelf life.
How proteins are maintained in a multi-dose dry powder formulation

A dry powder formulation relies primarily on lyophilization to maintain the integrity of the rhGH.

Lyophilization is a well-established method that stabilizes proteins during storage. Lyophilization is a process where water is removed from the formulation. By removing water, the degradation of the protein is reduced. Lyophilization has been used to store rhGH for more than 20 years.

While in storage before use, lyophilized formulations do not require preservatives due to the low likelihood of contamination and degradation. However, once a multi-dose cartridge has been pierced with a needle, it requires a preservative, whether it contains a lyophilized or liquid formulation.

Maintaining the rhGH in a dry powder as opposed to liquid has the following implications to the formulation:

- No surfactants are required.
- No preservatives are required prior to reconstitution.
Injection Volumes: Genotropin 12 mg Cartridge has the lowest injection volume of the most commonly prescribed rhGH products

* Table compares the highest concentration available for each product. The highest concentration formulation gives the lowest injection volume possible for each brand.

Notes:

Data not available for Zomacton 4 mg.

Source of data is US Package Insert.10–15

Genotropin® is a registered trademark of Pfizer, Inc. Humatrope® is a registered trademark of Eli Lilly and Company. Norditropin® Simplexx® is a registered trademark of Novo Nordisk Pharmaceuticals, Inc. Nutropin AQ® is a registered trademark of Genentech, Inc. Saizen® and click.easy® are registered trademarks of Serono Inc. Zomacton® is a registered trademark of Ferring Pharmaceuticals Limited.

No comparative, head-to-head studies have been done between GENOTROPIN® and other growth hormones in regard to the data presented here. Their clinical significance is unknown.
### Inactive Ingredients

Inactive ingredients per 10 mg of rhGH*

WFI (Water For Injection) represents the milligrams of water required

<table>
<thead>
<tr>
<th>Inactive ingredients (milligrams)</th>
<th>Genotropin® 12 mg cartridge</th>
<th>Nutropin AQ® 10 mg/2 ml</th>
<th>Norditropin® SimpleXx 15 mg/1.5 ml</th>
<th>Humatrope® 24 mg cartridge</th>
<th>Saizen® 8 mg click.easy</th>
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</thead>
<tbody>
<tr>
<td>Buffer</td>
<td>0</td>
<td>+819 mg WFI</td>
<td></td>
<td></td>
<td>+1715 mg WFI</td>
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<tr>
<td>Stabilizer</td>
<td>+1000 mg WFI</td>
<td>+1250 mg WFI</td>
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<td></td>
<td></td>
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<tr>
<td>Bulking agent</td>
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<tr>
<td>Surfactant</td>
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</tr>
<tr>
<td>Preservative</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Tonicity adjuster</td>
<td></td>
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</tr>
</tbody>
</table>

* In order to compare different cartridge/vial sizes the data shown has been normalized to 10mg of rhGH. Table compares the highest concentration presentation available for each product.

Notes:

Quantities of inactive ingredients are not provided in the Package Insert (US) or Summary of Product Characteristics (EU) for Zomacton.

Source of data is US Package Insert.10–15

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Preservatives

Preservatives per 10 mg of rhGH*

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pH Value

Values of pH for major commercially available rhGH

Notes:

- pH value not provided in the Package Insert (US) or Summary of Product Characteristics (EU) for Zomacton.
- Saizen and Norditropin SimpleXx provide a pH range only.

Source of data is US Package Insert,10–15 except for Norditropin SimpleXx which is the Norditropin SimpleXx Product Monograph August 1999.

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REFERENCES


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