Synovea® HR
Asyntra™ SL
Safe & Highly Effective in Controlling Skin Pigmentation
Alkylresorcinols are amphiphilic phenolic lipids present in significant amount in the bran fractions of rye and other cereals. 4-Hexylresorcinol (HR) is the most studied and well-known alkylresorcinol, which has an 80-year history of use in food & pharmaceuticals. HR has a GRAS status and is considered to be safe and effective in use as an anti-browning dip for shrimp and fresh cut fruits. Synovea®HR Hexylresorcinol with a purity of >99% is developed for skin care applications. Synovea®HR has been clinically proven to be four-times more effective than Hydroquinone in lightening skin. This result along with its anti-glycation and stimulatory effects on cell protective glutathione and antioxidant defense enzymes made Synovea®HR a key ingredient of choice in many skin brightening, anti-aging, skin protection and even-toning products. Synovea®HR has not been tested on animals.

### Product Information

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Synovea®HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>INCI Name</td>
<td>Hexylresorcinol</td>
</tr>
<tr>
<td>CAS #</td>
<td>136-77-6</td>
</tr>
<tr>
<td>ELINCS</td>
<td>N/A</td>
</tr>
<tr>
<td>Harmonized Tariff #</td>
<td>205-256-4</td>
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<tr>
<td>Appearance</td>
<td>White to off-white to pinkish powder; May become soft lump</td>
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<tr>
<td>Assay (HPLC)</td>
<td>Minimum 99% Hexylresorcinol</td>
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<tr>
<td>Solubility</td>
<td>Highly miscible with a wide range of hydrophobic emollients and solubilizers</td>
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<tr>
<td>Suggested use level</td>
<td>0.5 to 1%</td>
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<tr>
<td>REACH pre-registration#</td>
<td>TN148738-05</td>
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<td>Patent Status</td>
<td>USPA20080305059, WO2008/153629</td>
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<tr>
<td>Storage</td>
<td>Store in original, sealed container at +10 to +30 0C; avoid light, heat &amp; moisture</td>
</tr>
</tbody>
</table>

### Safety Data: Synovea®HR

- The European Union (EU) Council of Ministers has approved hexylresorcinol as a new additive as safe to use in EU foodstuffs (June 2006; Source: Keith Nuthall). Safety Information obtained from EUROPEAN COMMISSION, HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL, Scientific Committee on Food SCF/CS/ADDCONS/50 Final Opinion of the Scientific Committee on Food on 4-Hexylresorcinol (expressed on 5 March 2003)
- **Acute Oral LD₅₀**: The oral LD₅₀ of hexylresorcinol in the rat, rabbit, guinea pig and dog ranged from 550 to >5000 mg/kg body weight
- **Subacute toxicity**: Oral doses up to 500 mg/kg to mice and rats showed reduced body weight only for male rats. No other relevant compound-related findings were noted
- **Allergenicity/skin irritation/skin sensitization**: Tests in guinea pigs showed that hexylresorcinol was non-sensitizing when applied topically. HRIPT (1, 2 & 5% in corn oil, Total subjects 240) demonstrates it to be a non-primary irritant and a non-primary sensitizer (Sytheon data; Work done by Cantor Research Lab, Blauvelt, NY)
- **Skin-irritating propensities** using 0.1% and 0.5% level on scarified skin: Showed low irritating potential and compares well with saline control (Sytheon data; Work done by Product Investigations, Inc., Conshohocken, PA)
- **Carcinogenic potential**: Daily use of hexylresorcinol mouthwashes did not show any association with oral cancers in women. Committee considered that hexylresorcinol is not carcinogenic. Carcinogenic potency projects (http://potency.berkley.edu/). No positive for rat & mouse target sites (both males & females). No positive for rat & mouse determined by TD₅₀ (mg/kg/day)
- **Possible antineoplastic agent**: Inhibition of some spontaneous tumors by hexylresorcinol [Chaabra et al, Fundam Apl Toxicol, 11(4):685-690, 1988]
**In-vitro Melanin Inhibitory Activity of Synovea®HR**

**Synovea®HR inhibits melanin production**

Protocol:
- Cultured B16 melanocyte cells in DMEM supplemented with 10% calf serum
- Incubated with Synovea®HR for 72 hrs
- Photographed cultures to show the effect in the extracellular melanin production: control vs. product
- Counted cells and quantified melanin level by measuring absorbance at 490 nm

**In-vitro Enzyme Inhibitory Activity: Synovea®HR vs Commercial Products**

**CONCLUSION**

Synovea®HR has the most effective melanin inhibitory (in-vitro) activity over other well known commercial products

*Only address natural & hyper-pigmentation...not tattoos*
Human Skin Lightening Clinical Study: Synovea® HR vs. Hydroquinone

Skin lightening effectiveness of 0.5% Synovea®HR compares well with 2% Hydroquinone. Synovea®HR is four-times more effective than Hydroquinone. The results are highly significant statistically: p-value <0.05 (4 weeks); <0.005 (8 weeks).

Skin Protective Properties of Synovea® HR

- **Cell Protection**: Upregulating Glutathione, Glutathione peroxidase, Glutathione reductase
- **DNA Protection**: Providing long-term protection of DNA; Practically no DNA degradation even under UV-light
- **Protein Protection**: Protecting Collagen and other proteins by reducing Glycation

FORMULATION GUIDELINES

Synovea® HR as well as Asyntra™ SL will remain white in appearance in formulated products. At 45°C for two months & > 2 years at RT, lotions containing 0.5 to 1.0% Synovea® HR and 2 to 4% Asyntra™ SL showed practically no color shift. A series of aesthetically pleasing and stable formulation have been developed with these two products.

- **Synovea® HR**: Highly soluble in Capric/Caprylic triglycerides, Ethyl linoleate, and other esters, non-ionic solubilizers, glycerol and a wide-range of glycols.
- **Asyntra™ SL**: Miscible with a variety of ester emollients and solubilizers.

- **Use level of Synovea® HR**: 0.5 – 1.0% (w/w) and Asyntra™ SL: 1.5 to 4% (w/w) of finished formulations
- **Dissolve** 0.5 g of Synovea®HR in about 2 g of ethoxydiglycol or butylene glycol or propylene glycol and add to the formulation after making emulsion, preferably at about 50°C. Alternately, one could add Synovea®HR in the oil phase. For Asyntra™ SL, the product can be added directly to the oil phase or after making the lotion while cooling at ~40°C.
- **For preparation of serum or transparent gel**, use non-ionic solubilizers having high HLB values. Use PEG-40 hydrogenated castor oil, Laureth 23, Polysorbate 20 or 80 to solubilize Synovea®HR.
- **Addition of a small amount of disodium EDTA (~0.1%) resolves the coloration problem, if any, due to the presence of iron or copper.**
- **The finished product** must be acidic, preferably having pH below 6.5.
- **Formulations containing Synovea® HR or Asyntra™ SL may cause drop in viscosity.** Acidic (such as, Xanthan gum) or neutral thickeners (such as, Cellulosics) are good for maintaining desired viscosity.
- **The finished product** should be protected from prolong exposure to heat and light.
Asyntra™SL

Synovea®HR, the key component of Asyntra™SL, has been clinically proven to be four-times more effective than Hydroquinone. Utilizing the value of synergism, Sytheon has now developed Asyntra™SL by blending Synovea®HR and Ethyl linoleate in a skin friendly caprylic/capric triglycerides emollient.

Ethyl linoleate has been found to be an excellent solubilizer for Synovea®HR. Linoleic acid (LA) has been reported to be an essential fatty acid needed for skin nourishment; lightens UV-induced skin pigmentation and works by accelerating proteolytic degradation of tyrosinase.

Asyntra™SL is a clear liquid, very effective and easy to use. The product has not been tested on animals.

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Asyntra™SL</th>
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<tbody>
<tr>
<td>INCI Name</td>
<td>Caprylic/Capric Triglycerides and Hexylresorcinol and Ethyl Linoleate</td>
</tr>
<tr>
<td>CAS #</td>
<td>65381-09-1; 136-77-6; 544-35-4</td>
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<tr>
<td>ELINCS</td>
<td>265-724-3; 205-256-4; 208-868-4</td>
</tr>
<tr>
<td>Appearance</td>
<td>Clear yellow to yellowish liquid</td>
</tr>
<tr>
<td>Assay (titration)</td>
<td>24 – 27% (w/w) of Hexylresorcinol</td>
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<tr>
<td>Solubility</td>
<td>Highly miscible with a wide range of hydrophobic emollients and solubilizers</td>
</tr>
<tr>
<td>Suggested use level</td>
<td>level 1.5 to 4%</td>
</tr>
<tr>
<td>Storage</td>
<td>Store in original, sealed container at +10 to +30 °C; avoid prolong exposure to light &amp; heat</td>
</tr>
</tbody>
</table>

Safety Data: Asyntra™SL

In classical toxicological terms, Asyntra™SL is practically non-toxic to humans and other animals because all three ingredients present in Asyntra™SL have long history of safe use in personal care applications.

Human Repeat Insult Patch Test (HRIPT) at 10% dilution in corn oil showed Asyntra™SL to be non-primary skin irritant and non-primary skin sensitizer.
In-vitro Melanin Inhibitory Activity of **Asyntra™SL**

% Reduction in Melanin VS. Control

Protocol:
- Cultured B16 melanocyte cells in DMEM supplemented with 10% calf serum
- Incubated with Asyntra™SL for 72 hrs
- Photographed cultures to show the effect in the extracellular melanin production: control vs. product
- Counted cells and quantified melanin level by measuring absorbance at 490 nm

**Results:**
- Asyntra™SL reduces 40% extracellular melanin
- Asyntra™SL reduces 35% intracellular melanin

**Human Skin Lightening Clinical Study with Asyntra™SL**

Measurement of ITA* Before & After treatment

Protocol:
- Subject: 15
- Race: African-American, and Hispanics
- Test Size: Full Face
- Product: 1% Asyntra™SL lotion (no sun screen!)
- Application: Twice a day
- Study Duration: 8 weeks

**Results:** Statistically significant skin lightening (*p value <0.05*) with Asyntra™SL

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Ethyl Linoleate in Asyntra™SL is involved in post translational degradation of Tyrosinase. All other sites in the melanogenesis pathways are inhibited by Hexylresorcinol.
Disclaimer

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