SENSITIVE SKIN
FROM DIAGNOSIS TO SOLUTIONS

SCC, February, 23rd 2016
Veronique Maurin
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Sensitive Skin

What is it?

Sensitive skin:

- Is a complaint, originally defined as a minority and now claimed by a majority of women in industrialized countries and nearly half of men.

- Is one of the most common disturbing skin conditions with high impact on life quality.

- Is a term used by individuals who perceived themselves to have more reactive facial skin to applied products and/or environmental factors than the general population.

- Represents a syndrome of physiological reactions NOT a disease entity.

Sources:
- S. Ständer, S.W. Schneider, C. Weisshaupt, T. A. Luger, L. Misery; "Putative Neuronal Mechanisms of Sensitive Skin"; Experimental Dermatology 2009
Sensitive Skin

What is it?

Sensitive skin:

◦ Describes a condition of the skin defined by:
  
  ➢ Sensory sensations: tightness, stinging, pricking, burning, tingling, pain and less frequently itching mainly on the face
  
  ➢ Symptoms: erythema and flush/redness

◦ Is a hyper-reactive skin, characterized by exaggerated sensorial reaction to environmental or topical factors, including hard water and cosmetics

◦ The degree of skin sensitivity depends on the individual

Sources:
• S. Ständer, S.W. Schneider, C. Weisshaupt, T.A. Luger, L. Misery.; "Putative Neuronal Mechanisms of Sensitive Skin"; Experimental Dermatology
Sensitive Skin

Typology

Sensitive skin is:

- with **age** (as facial sensitive epidermal nerve density is also decreasing while skin ages predicts an increased susceptibility to irritants due the barrier impairment)
- with **spicy food** (rich in capsaicin)

++ on **Face**

+ on other areas involved: **hands, scalp, feet, neck, torso, back** …

**INDEPENDENT** on **gender**

**INDEPENDENT** on **ethnicity**

Yet ++ on **young women**

Sources:
- S. Ständer, S. W. Schneider, C. Weisshaupt, T. A. Luger, L. Misery.; “Putative Neuronal Mechanisms of Sensitive Skin”; Experimental Dermatology 2009
## Epidemiologic Studies

**Market Opportunities**

A big concern, a global growing potential

- Rates of skin sensitivity have increased steadily over time, particularly among men
- Higher prevalence of Self-Declared Sensitive Skin:

  ➢ **EU, the US and Japan:**
    - Approx. 50% of women
    - Approx. 30% of men

  ➢ **China:**
    - Approx. 36% of the population

### Sources:
- S. Ständer, S.W. Schneider, C. Weisshaupt, T.A. Luger, L. Misery, "Putative Neuronal Mechanisms of Sensitive Skin", Experimental Dermatology 2009
Sensitive Skin

First Consumer Insights

— Globally, 53% of consumers claim to have sensitive skin

— 68% of consumers across the world state that their skin is more sensitive than a few years ago

— Visible signs (redness, blotches, unevenness, bumps) are socially the most embarrassing & need to be treated in priority.

CMI Data Source: Symrise Cosmetic Ingredients consumer data base
Sensitive Skin

Consumer Market Insights

— Having sensitive skin is widely lived as a handicap

— Sensitive skin:
  — can be associated to other problems which appear as causes, consequences … or complications (acne, combination skins …)
  — is defined, conversely to dry or oily skins, by its instability
  — The focus is not limited to the face but includes many other body zones

CMI Data Source: Symrise Cosmetic Ingredients consumer data base
Sensitive Skin
Consumers Market Insights

3 types of concerns:

♦ **Anger:** 43% of Chinese consumers describe their skin as “a sensitive skin”: they want to do something about it. It is annoying, frustrating and gets on their nerves.

♦ **Visible signs:** Redness (flushes, red cheeks…), Dull complexion, Rashes, Dehydration, Thinness of skin

♦ **Sensorial signs:** Tightness, Tingling/Stinging, Scratching

*Sources: Symrise CMI Data Source – Symrise Cosmetic Ingredients Consumer Data Base
LE Consumer Database 2012 (12,500 interviews in Brazil, China, France, Germany, USA)
Global Sensitive Skin Exploration 2012 (including Chinese female focus groups 20-30 & 35-45 y.o.)
Global Aging Exploration 2012 (including Chinese female focus groups 18-25, 25-35, 35-50 and 50-65 y.o.)
Women Identify Specific Causes  
*In Total They Focus on Four Causes*

**N° 1: Climatic harshness**
- Temperature changes: Cold, Wind, Heat
- Various pollutions
- Air quality
- Car fumes, Toxic particles, Dust
- Sun
- Water quality
- Impurities, Chlorine, Hard water

**N° 2: Stress. Emotions**
- Too fast pace
- Work, Conflicts
- Anxiety

**N° 3: Bad food**
- Sweets. Chocolate
- Fats
- Sodas & acids
- Additives
- Alcohol
- Spices

**N° 4: Cosmetics**
- Aggressive procedures
- Fragrances, Chemicals

**Women Specific**

**Common**

**Most frequent**

**Less frequent**
Men Identify Specific Causes

In total they focus on five causes:

**N° 1: Shaving**
- Mechanical irritation
- Blades
- After-shave

**N° 2: Genetics**
- Predispositions
- Role of allergies

**N° 3: Climatic harshness**
- Heat
- Air quality
- Car fumes
- Toxic particles
- Dusts
- Sun

**N° 4: Lifestyle**
- Cigarettes
- Food: fat/sweet
- Lack of sleep
- Clothes/ fibers
- Detergents

**N° 5: Cosmetics**
- Alcohol
- Fragrances
- Hard/too hot water

**Men Specific**

**Common**

**Most frequent**

**Less frequent**
Sensitive Skin

Consumer Expectations

Innovative products vs. visible and sensorial signs

Soothing remedies for peace, energy & beauty

Inside out action: moisture & nurture

Purity and minimized risks of allergy

Reinforced skin barrier & repair

CMI Data Source: Symrise Cosmetic Ingredients consumer data base
Sensitive Skin Products

Market Evolution @ A Glance

1. MINIMISING RISKS
2. REPAIRING
3. NORMALISING

Towards Innovation

Standard
Existing Solutions

1st Generation

**HIGH TOLERANCE FORMULA**
- Specifically formulated for sensitive skin, "free of" the most obvious irritants: fragrance free / paraben free / alcohol free / colorant free etc.
- Dermatological claims (e.g. hypoallergenic)

**SOOTHING INGREDIENTS**, combined to skin-friendly formulas
- **BOTANICALS** - Rose water, witch hazel etc.
- **THERMAL WATER** - Focus on soothing benefits

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**HIGH TOLERANCE FORMULA**
- Garnier CleanSensitive Anti-Tightness Milk
- Estée Lauder Vérité Calming Fluid

**BOTANICALS**
- Avon Sensitive Face Cream Chamomile and Poppy

**THERMAL WATER**
- Vichy Aqualia Thermal

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**MINIMISING RISKS**
Existing Solutions

2nd Generation

ACTIVES (natural or nature-inspired) - Major ones, often acting on redness symptoms:
- from α-Bisabolol to Bisabolol + Zingiber Officinale Root Extract (ID367692)
- Allantoin
- Avena Sativa (Oat) Kernel Extract
- etc.

CLARINS
Extra Firming Lips & Contour Gentle Exfoliator with Bisabolol

AVEENO
Ultra-Calming - with Avena Sativa (Oat) Kernel extract

YVES ROCHER
Active Sensitive - Allantoin

2
REPAIRING
Existing Solutions

3rd Generation

NEURO-SENSORIAL WORLD
A New Generation of Actives working at the cell communication level
- Hydroxyphenyl Propamidobenzoic Acid (ID143535)
- 4-t-Butylcyclohexanol (ID399944)

... THE NEXT GENERATION OF SENSITIVE SKIN PRODUCTS

VITASKIN PHARMA
Protective Anti-redness Day Cream

Dr BAELTZ
Antia Moist Balancer 2000 Super Sensitive

INDEED LABORATORIES
Retinol Reface

MANTECORP (Hypermarcas)
Epidrat Calm

BDF
Eurecnn Ultra Sensitive 0%
Irritation & Inflammation

**Definition**

**Causes**
(eg. chemical, physical, mechanical, external factors ...)

**Irritation**

- Burning
- Stinging
- Itch
- Pain

**Vicious circle**

**Inflammation**

- Redness
- Edema
- Heat

**Neurosensorial irritation**

Sources:
- Sensitive skin syndrome, Dermatology: clinical & Basic Science Series, Edited by Enzo Berardesca, Joachim W. Fluhr, Howard I. Maibach
Sensitive Skin
What’s happening inside?

**1. DAMAGES IN SKIN BARRIER**
- Loss of NMF, lipids, proteins etc.

**2. RELEASE OF PRO-INFLAMMATORY FACTORS**
- Keratinocytes
- Mast cells
- Sensory nerves
- Heat receptors
- Change in nerve sensitivity

**3. BURNING / STINGING / TIGHTNESS**
- Excessive activation of heat receptors
- Release of itching mediators

**4. REDNESS**
- Release of pro-inflammatory mediators

**5. WEAKENED SKIN BARRIER**
- Increased susceptibility to external factors

**6. DRY, SENSITIVE SKIN**
- Change in keratinocyte proliferation & differentiation

**7. SENSITIVE SKIN**
- Mechanical factors (shaving, waxing, hair dryer etc.)
- Physical factors (sunlight, temperature, humidity etc.)
- Chemical factors (depilatories, retinol, preservatives etc.)

**Epidermis**
- Stratum Corneum
- Stratum Lucidum
- Stratum Granulosum
- Stratum Spinosum
- Stratum Basale

**Dermis**
Skin
Cellular Communication

- 3 keys players in cutaneous response to irritants: **Keratinocytes**, **Nerve cells** & **Mast cells**
- Expression of sensory receptors and neuropeptides regulating the neuro-immuno-cutaneous system

**Reaction cascade:**
- **Keratinocyte**
  - Langerhans cell
- **Sensory nerves**
  - T cell
  - Dendritic cell
  - Fibroblast
- **Mast cell**
  - Macrophage
  - Monocyte

**Sources:**
Skin Barrier Impairment

BIO391* / ID445662**

Skin Mechanisms of Action
- Deficiency in key SC lipids & structural integrity
- Hyper proliferation & shedding of keratinocytes
- Decrease of hydration level

Skin Reactions
- Barrier impairment
- Water loss & dry skin

Symrise Solution
- Barrier repair & topical applications of lipids with
  BIO391 / ID445662

*INCI: Cetylhydroxyproline Palmitamide
** INCI: Hexyldecanol, Bisabolol, Cetylhydroxyproline Palmitamide, Stearic Acid, Brassica Campestris (Rapeseed) Sterols
Skin Barrier Impairment

BIO391 / ID445662

♦ Ceramides: important constituent of the lipid bilayer
♦ Permeability barrier: corneocytes enveloped by lipid bilayers

„Brick and Mortar“ - Model (P.M. Elias)

Corneocytes are the bricks, the lipid bilayers are the mortar
BIO391 is a new, synthetic ceramide
Its structure is similar to natural Ceramide 2

Major advantages of BIO391:
- Very low melting range
- Easy to formulate
- Non-apoptotic (unlike other ceramides)

Compound Melting range:
- Ceramide 2: 90 -105 °C
- Ceramide 3: 120 -130 °C
- BIO391: 53 - 59 °C
Barrier Repair – SDS Model
BIO391 / Dose Response Results

- Clinical study 20 human subjects with winter-dry skin
- Test parameters: TEWL: major indicator of barrier integrity & Redness: erythema, indicator of irritation
- Skin barrier disruption by treatment with 2% SDS for 24h (occlusive)
- Application of test products (2 mg/cm²) twice daily for 5 days on volar forearm
- Measurements on 1 day before SDS treatment (D-1) & days 3 & 5

Barrier integrity (%) on day 5 after SDS damage (based on TEWL)

- Optimum barrier repair efficacy with 1% BIO391
- Optimum barrier repair efficacy – up to 80% @ 0.1%
Biochemical Consequences of a Weakened Barrier

- Cutaneous barrier perturbation stimulates cytokine production in the epidermis of mice. Moreover, the mRNA levels for epidermal IL-1a, IL-1b and GM-CSF also were elevated 7-fold over controls, after either acetone treatment or tape stripping. 

- Stress induced changes in skin barrier function in healthy women. The interview stress caused a delay in the recovery of skin barrier function as well as increases in plasma cortisol, norepinephrine, IL-1b and IL-10, TNFa,…

- Epidermal interleukin-1 alpha generation is amplified at low humidity: implications for the pathogenesis of inflammatory dermatoses. …the amount of IL-1a in the epidermis was higher in animals kept in a low-humidity environment than in a high-humidity one.

➔ Anti-irritants support epidermal barrier repair
BIO391 Synergism with Bisabolol

**TEWL**

Barrier integrity (%) on day 5 after SDS damage (based on TEWL)

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<th>Condition</th>
<th>Barrier Integrity (%)</th>
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<tr>
<td>Untreated, undamaged</td>
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<tr>
<td>Untreated</td>
<td>45</td>
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<tr>
<td>Placebo</td>
<td>51</td>
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<tr>
<td>0.1% Bisabolol (A)</td>
<td>51</td>
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<tr>
<td>0.1% BIO391 (B)</td>
<td>55</td>
</tr>
<tr>
<td>0.1% (A) + 0.1% (B)</td>
<td>73</td>
</tr>
<tr>
<td>1.0% BIO391</td>
<td>69</td>
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* = p < 0.05 compared to Placebo

Synergistic effect of 0.1% BIO391 and 0.1% Bisabolol ➔ 73% Barrier repair!
BIO391 Synergism with Bisabolol

Redness

Erythema reduction (%) on day 3 after SDS damage

Synergistic effect of 0.1% BIO391 and 0.1% Bisabolol
Redness / Erythema

Release of key inflammatory cytokine IL-1α from keratinocytes, macrophages...
  ➔ biosynthesis of other proinflammatory mediators
  ➔ increase in blood flow vascular permeability

Formation of lipid mediators (Prostaglandins, Leukotriens, Platelet Activating Factor) from keratinocytes

SKIN MECHANISMS OF ACTION

SKIN REACTIONS

REDNESS & ERYTHEMA

SYMRISE SOLUTION

Anti IL-1α & TNFα & PGE-2, LTB4 with ID367692

* INCI: Bisabolol, Zingiber Officinale (Ginger) Root Extract

- IL-1α: Interleukin 1 α
- TNFα: Tumor necrosis factor α
- PGE-2: Prostaglandin E2
- LTB4: Leukotrien B4
Clinical Study
Protocol

♦ Test Products:
  > vehicle (Placebo)
  > vehicle + ginger extract (10 ppm)
  > vehicle + bisabolol (1000 ppm)
  > vehicle + 0,05% ID367692
  > Subjects: Number of individuals: 20
♦ Test Area: Inner sides of forearms

♦ Application: 4-6 h after SDS treatment, then for 7 days, twice daily

♦ Evaluation:
  > Before treatment with SDS
  > 4-6 h after SDS treatment
  > 4-6 h after the last daily application on day 1, 2, 3, 5 and 7

♦ Skin Parameter: Skin Redness
ID367692

Boosted relief with -50% of redness in 2 days!

SYNERGISTIC EFFECT OF ID367692 = Bisabolol + Ginger Extract

Clinical Study – SDS Erythema

- 50%

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<th>Day 0 after SDS</th>
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<th>Day 2</th>
<th>Day 3</th>
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<td>0.05% ID367692</td>
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<td>60</td>
<td>50</td>
<td>40</td>
<td>30</td>
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* p < 0.05 vs Placebo
* p < 0.05 vs Placebo & synergistic
Neuro Sensory Irritation

**Definition**

There is a link between neuro sensory discomfort (eg burning, stinging, itching, tightness …) and the self perception of sensitive skin:

♦ Sensitive skin could be related to a physiological mechanism involving sensitive epidermal nerves as sensitive skin subjects demonstrate a significant higher skin hyper-reactivity to capsaicin

♦ Sensitive skin leads to a lowering skin’s tolerance threshold which is not directly related to any immunological or allergic mechanism

♦ Impaired skin barrier function together with an increase in transepidermal water-loss underlie sensitive skin

* Sources: S.Ständer, S.W.Schneider, C.Weisshaupt, T.A.Luger, L.Misery.; "Putative Neuronal Mechanisms of Sensitive Skin"; Experimental Dermatology 2009
Cross talk between dermal mast cells and cutaneous neurons

Mast cell

TNFα

SP

Histamine

Tryptase

PAR-2

Histamine 1 receptor

Neurokinin 1 receptor

Proteinase activated receptor-2

Tumour necrosis factor receptor

Heat, PGE-2, ...

Nerve endings
SKIN MECHANISMS OF ACTION

Release of itch mediators (Histamine, tryptase & TNFα) from mast cells.

SKIN REACTIONS

ITCHING

SYMRISE SOLUTION

Anti histamine release with **ID143535**

* INCI: Butylene Glycol, Pentylene Glycol, Hydroxyphenyl Propamidobenzoic Acid
**ID143535**

*Proven efficacy by inhibiting histamine release*

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**INHIBITION OF HISTAMINE RELEASE**

*In Vitro Study*

A study to determine the effect of ID143535 on Histamine net release from peritoneal mast cells stimulated by substance P (10µmol).

**Secreted histamine quantified by measuring the fluorescence intensity using a spectrofluorometer**

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**Graph:**

ID143535 inhibits Histamine net release from peritoneal mast cells, stimulated by substance P.
ID143535

65% itching reduction sensation!

Clinical Study Protocol:
- 40 subjects (35-80 years) with visible dry skin and itching
- 4 weeks double blind study - subjects use one product for 2 weeks and cross over to use the other product for the next 2 weeks
- Test products (double-blinded): Emulsion A (vehicle) & Emulsion B with 2% ID143535
- Measurement time points: Baseline - week 2 (study cross over point) & week 4
- Parameters: scaling (10 point ordinal scale; 0 - none & 9 - severe); erythema & Itch

Statistically significant reduction of itch by 65% with ID143535!
**ID143535** significantly reduces the clinical symptoms associated with dry itchy skin. Reduction of these parameters confirms that the subjects have perceived a decrease in itching, since the visual skin attributes usually improve concurrently with symptoms.
Burning & Stinging – TRPV1

* INCI: Pentylene Glycol, 4-t-Butylcyclohexanol
Burning & Stinging

TRPV1 Receptor

TRPV1 (trans potential vanilloid receptor 1):

- is a 6-transmembrane protein assembled as functional tetramers
- is a major contributor to the enhanced thermal responsiveness observed after cutaneous inflammation
- is activated by eg. prostaglandins (PGE-2) and nerve growth factor (NGF) by lowering the activation threshold
- is stimulated after topical capsaicin application and transmits burning, pain or burning pruritus
- accelerates the Ca2+ flux into the cell when activated, thereby significantly increasing heating symptoms

TRPV1 : main contributor to the sensory symptoms observed sensitive skin.

* Sources:
  S.Ständer, S.W.Schneider, C.Weissshaupt, T.A.Luger, L.Misery.; "Putative Neuronal Mechanisms of Sensitive Skin"; Experimental Dermatology
TRPV1 Expression
A Key Player

TRPV1 : the best characterized receptor in the epidermis highly expressed in sensitive skin

High levels of TRPV1 in over sensitive skin

Undetectable levels in non sensitive skin

Low levels of TRPV1 in normal skin

Tissues collected from a subject at limb amputation
Facer et al. BMC Neurology 2007, 7:11
**ID399944**

**Cosmetic Intolerance Syndrome – in vivo Study**

- **PROTOCOL**
  - 20 subjects
  - 1.2 % ID399944 in o/w emulsion

Selection of subjects

- Sting test

Assessment 1 & 3 min after treatment

- Noxious sensory stimulation at D1 & D5
  - [Sauna exposure + lactic acid sting test]

Application of the O/W emulsion - Active versus placebo

- Day 1
- Day 2
- Day 3
- Day 4
- Day 5

- Treatment (5 days – 8 applications)

**Statistical Analysis**

- ID399944 immediately reduces facial irritation seen in persons with CIS
- Immediate effect -65% versus placebo!!
- ID399944 immediately reduces facial irritation seen in persons with CIS
- … Improves skin tolerance & resilience!

- Statistically significant reduction in overall facial irritation (p=0.03)
- Immediate effect -65% versus placebo!!

* p < 0.03 Significant

- Moment of truth!
  - -65%
  - -25%
  - -20%