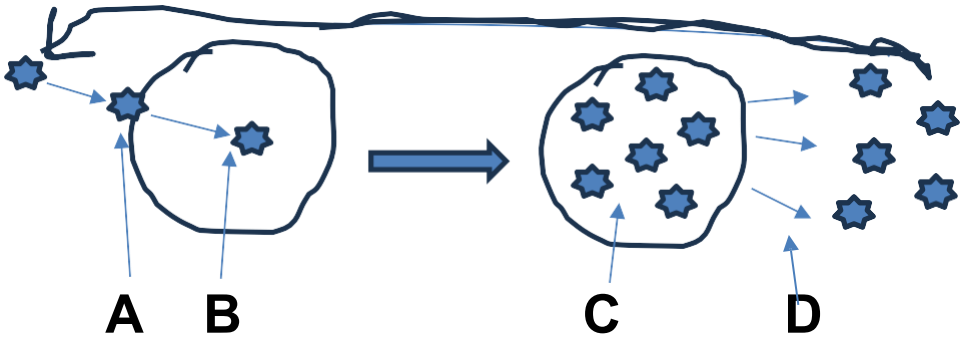
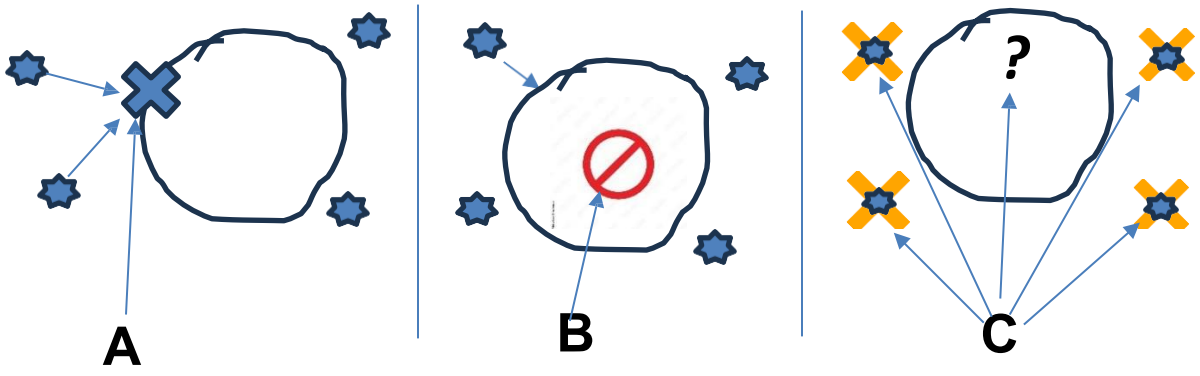
FOR THE HEALTHCARE PROFESSIONAL

Stages of Viral Infection



A- Viral Fusion to cell membrane
B- Viral Entry into cell
C- Viral Replication (intracellular – in the nucleus)
D- Viral Exit from cell (exocytosis) newly formed virions are now able to infect more cells → repeat steps A, B, C & D, generating exponential replication

Therapeutic Viral Targeting



A- Docosanol – Extracellular effect - blocks viral fusion with cell membrane
Viral particles (virions) are not killed → potential to spread

B- Antiviral Medications (e.g., nucleoside analogues) - Intracellular effects

Block viral DNA replication → block viral replication

Any remaining extracellular virions remain viable → potential to spread

C- Zap-H™ - Extracellular (? intracellular)- dissolves into / disrupts viral envelope

→ Virions ——— Not capable of reproducing or spreading

- **No Viral Fusion**
- **No Viral Entry or Replication**
- **No Viral progression to other cells**

UNDERSTANDING THE HERPES VIRUS

BACKGROUND ON THE COLD SORE VIRUS

Herpes Virus Replication

The enveloped virus first binds to and then enters a cell in the body. After viral entry, the virus replicates rapidly inside the host cell. The herpesvirus particles (virions) develop a protective outer envelope by taking a part of the host cell membrane as they exit the host cell – this process is called exocytosis. The greatly expanded number of viral particles that are released from the cell can now spread to other cells, repeating the replication process. In this way, the virions expand exponentially at a rapid pace.

The herpes virus is classified as a DNA virus and an enveloped virus. Viral DNA is stabilized by a shell of proteins called the capsid. Together the DNA and capsid are referred to as the nucleocapsid. The nucleocapsid is surrounded by the outer envelope. The virion's outer envelope surrounds & protects the inner nucleocapsid.

The viral particle is always surrounded by this envelope except after it enters a cell, whereby the nuclear material, nucleocapsid, is released. The released nucleocapsid enters the host nucleus, wherein lies the host DNA. In the nucleus the viral DNA replicates by manipulating and utilizing host cell machinery for this process. After subsequent release from the nucleus, the newly formed nucleocapsid particles fuse with the host cell membrane. In a process referred to as exocytosis the newly formed and expanded nucleocapsid particles "bud off" from the host cell plasma membrane, incorporating a piece of the host cell membrane which forms the viral envelope. In this way, the viral envelope is acquired from the host cell plasma membrane. The viral envelope being formed from host cell membrane helps it evade the immune system – i.e., the immune system views this envelope as normal cellular tissue.

Why cold sores, also called fever blisters, may be difficult to treat.

The herpes HSV1 virus is the main cause of cold sores/fever blisters on lips. A similar herpesvirus is HSV2, the main cause of genital herpes, but either one of these 2 versions can cause oral cold sores. A 3rd herpesvirus is human herpesvirus 3 (HHV3), also referred to as varicella (chickenpox), and it usually infects children, while its reactivation as an adult result in herpes zoster (HZ) or shingles. Herpesvirus owes its successful spread to its complexity, which has enabled it to effectively slow down the human immune system in several different ways. As discussed above, because the viral envelope is formed from the host cell membrane; it may not be viewed as foreign by the immune system.

Furthermore, glycoproteins of the herpesvirus envelope play a significant role in the early interactions, attachment, and entry of viral particles into the host cell. They modulate the immune system to maintain a presence in the infected host. They maintain a balance between preventing from being targeted and killed by the immune system, while at the same time preventing host cell death, as their survival depends on host cell survival.

Further yet, herpesvirus has evolved a mechanism by which to remain dormant in the body for long periods of time, wherein it can linger in a hibernation state known as viral latency. The herpesvirus (HSV1) has a predilection for neurons near the base of the brain, in an area called the trigeminal ganglion. The virus lies dormant within these nerve cells and can do so for months to many years, even 30 or more. It can be activated by numerous factors, and this may vary between individuals. Triggering factors include stress, lack of sleep, exposure to sun, cold wind, a cold, flu or other illness, a weak immune system, and changing hormone levels.

The cold sore early stage typically begins with a tingling sensation on the lip. Within 12-24 hours the early sore, a red bump develops. It then may take 1-2-3 days to form a blister(s), i.e., the cold sore. The sore may build up and then excrete a highly infectious clear/yellow liquid, the so-called “weeping phase.” The final phase is the formation of a scab, which can take 7-14 days to resolve, and up to several weeks in the immune compromised individual. Both the blister, and the subsequent scab that forms, can develop a microscopic biofilm, a shield that protects the virus from the local microenvironment. The protective biofilm challenges the body’s immune system to fight the virus and can also hinder certain treatments. This is yet another mechanism by which the herpesvirus evades the immune system and makes it difficult to target.

Why cold sore strategies have limited effectiveness.

Herpesvirus has developed methods by which to hide itself from the immune system. Strategies that target HSV1 have had limited success for one main reason - current methods do not target the virus directly. For example, many cold sore strategies focus on relieving the symptoms, namely itch, tingling and pain, wherein the effects are typically of temporary nature. Second, drug treatments are available that block viral entry into host cells, however there is no direct effect on HSV1, and the virions can survive. Third, drug treatments are available that prevent viral replication, but again the virions can survive; hence they can spread. A common denominator for all these methods is that they do not affect viral particles in a way that directly prevents their spread.

The immune system is left to deal with the virus on its own, where the lesions and subsequent scab typically last anywhere from 7-14 days, and up to 3-4 weeks in some cases, especially in an individual with a compromised immune system. Whereas strategies that focus on relieving symptoms have no effect on cold sore duration, treatments that block viral entry and those that prevent replication can slightly reduce the duration of a cold sore lesion.

There are limitations with current methods. For example, agents that block viral entry reduce the duration of a cold sore, but only on average 18 hours, i.e., < 1 day*. A 3/4 day of improvement is a relatively minor benefit for a lesion that can last 7-14 days, or longer in immune compromised individuals. [“..... median time to healing in 370 docosanol-treated patients was 18 hours shorter than observed in 367 placebo-treated patients.....” from: Sacks; et al; , J Amer Acad Dermatology. 2001, Aug;]

Second, antiviral medications, i.e., nucleoside analogues, have been shown to reduce symptoms or the presence of a sore by 2 days.
[“…. only reduces the healing process in little more than 2 days". From: Alvarez, Front Microbiol, 2020, Feb; 11:139].

2 days shorter duration is a relatively minor improvement for a lesion that can last 7-14 days, or longer. There are yet additional issues with these antiviral strategies.

A problem for both viral entry blocking agents and antiviral medications is that the results are best if it these are started within 24 hours, although they can be effective at 24-48 hours after onset of symptoms, i.e., the sensation of tingling of a small red discoloration along the lip line. After 2 days of symptoms, the viral particles have proliferated to the extent that further prevention becomes futile.

Antiviral medications are more effective in reducing duration of symptoms as compared to viral entry blocking agents. A problem with antiviral medications is that their overuse can lead to viral resistance to these medications, making the medications less effective, or even ineffective. The development of resistance is most common in immune compromised individuals who have a more difficult time in eradicating cold sores, and thus require more frequent use of viral medications, which leads to development of resistance.

The Zap-H™ Benefit

What's a viral envelope and why do I care?

The viral envelope (also called viral membrane) protects the HSV viral DNA and helps prevent immune system targeting. It is proposed herein that, by dissolving into and destabilizing the viral envelope with Zap-H™, it can then lead to disruption of the functional components of the virus rendering it incapable of spreading. It is well established that numerous fatty acids are able to disrupt viral envelopes [*Thormar]. These studies have been done in the laboratory setting and such claims of viral membrane disruption cannot be automatically equated to effects on living tissues in the human body. However, our experience with topical application of Zap-H™ has shown rapid disappearance of skin sores and this correlates with the rapid viral envelope disruption that occurs in the laboratory setting. Zap-H™ comprises such fatty acids that dissolve into and disrupt viral envelopes. This is not a drug effect, rather a “detergent-like” effect (see below) wherein the Zap-H™ formulation physically interacts with envelope compounds, leading to membrane instability and dissolution, in a manner analogous to that which occurs with synthetic detergents.

[*Thormar H, et al; Inactivation of enveloped viruses and killing of cells by fatty acids and monoglycerides. Antimicrob Agents Chemother. 1987;31(1):27-31. doi:10.1128/AAC.31.1.27.]

Mechanism of action and what it means?

Combining the information from laboratory studies and existing publications, it is thought that the key mechanism of action for Zap-H™ is the ability of its ingredients to physically dissolve into the protective viral envelope, which destabilizes the envelope. Once the viral envelope is disrupted it renders the virus dysfunctional, impeding its ability to spread. It is proposed herein that Zap-H™ acts as a biological detergent (bio-detergent), wherein it physically interacts with membrane components, leading to pore formation, membrane instability, and envelope dissolution. Such detergent-like action is not a drug effect. Furthermore, once the viral envelope is disrupted, this exposes the herpesvirus’ internal components, which theoretically can then be

targeted by the body's immune system. This theoretically gives the immune system the opportunity to eradicate the virus more effectively. Such an effect is theoretical and has not been proven or approved by the FDA.

NOTE** – ***Zap-H™ is NOT A DRUG

Zap-H™ is deemed a biologic detergent (bio-detergent) and is not a drug, having no drug-like effects. Moreover, a drug targets one specific biological pathway or molecule in a single type of microbe. Furthermore, a drug does not have a broad-spectrum effect. Rather, a single drug targets only one type of microbe. For example, a drug can be either antiviral, antibacterial or antifungal, but it does not target multiple types of microbes.

Detergents, on the other hand, have a broad-spectrum effect on numerous and varying types of microbes. Detergents act by disrupting the lipid-bilayer that is a part of the outer structure of microbial pathogens (e.g., bacteria, fungi, and/or mycobacteria) including the viral envelope. Furthermore, detergents do not target a specific biological pathway or molecule. Rather, they act by physical means, wherein they dissolve into the lipid-like microbial membrane, which disrupts its stability, rendering the microbe less pathogenic. This effect of detergents is identical in all microbial pathogens. Zap-H™ similarly has a broad-spectrum destabilizing effect on microbial membranes, and in this way, the effect is identical to synthetic detergents. Zap-H™ as a bio-detergent is an improvement over synthetic detergents as it consists of biological compounds found in nature that can be metabolized by the body, ultimately making Zap-H™ immensely safer to apply topically.

Furthermore, fatty acids/oils in Zap-H™ are also found in mother's milk, i.e., those fatty acids that disrupt microbial membranes. Because these the fatty acids/oils in Zap-H™ are also found in mother's milk, this further indicates that this is not a drug.

It has long been known that detergents disrupt microbial membranes, including viral envelopes. In one study it was shown that detergents squeeze the membrane envelopes and break them apart. Detergents bind to membrane components causing expansion and subsequent formation of pores on their surface until they completely fragment. (Dresser, et al; J Phys Chem Lett. 2022 Jun 9;13(23):5341-5350)

Such a viral envelope disruption by Zap-H™ is herein referred to as a "bio-detergent". However, the term "bio-detergent" herein differs from the historical utilization of the term "biological detergent". Moreover, "biological detergents" have typically referred to detergents that contain natural enzymes—such as protease, lipase, and amylase—that break down protein, fat, and starch-based stains (blood, food, grass) at low temperatures, making them highly effective for everyday laundry.

The term "bio-detergent" herein refers to the use of biological fatty acids, or oils, in combination with ingredients that result in a water-based emulsion, rather than the use of synthetic compounds, to dissolve into viral envelopes. Moreover, the mechanism of action for the Zap-H™ formulation is the same as for synthetic detergents, wherein the detergent ingredients physically interact with membrane molecules resulting in destabilization of the viral envelope structure. The difference is that the "detergent' compounds in Zap-H™ are biological. They are not synthetic chemicals, rather they are compounds found in nature and they can be metabolized by the body.

Furthermore, the water-based emulsion formulation in Zap-H™ is more effective when applied topically than any fatty acid or oil used alone due to better skin absorption and more rapid hydration. Fatty acids and/or oils alone have slower absorption, wherein a significant portion remains on the skin surface and can leave an “oily” feel.

While published research articles show viral envelope disruption by fatty acids, an associated skin sore response to fatty acids with topical application has not been evaluated by the FDA. However, the documentation of rapid viral envelope disruption by fatty acids in published articles correlates with our findings of rapid hydration and disappearance of skin sores after topical application of Zap-H™.

Effective even at 5 days post onset of symptoms

Our experience further shows that individuals using Zap-H™ anecdotally note that it is effective even if application begins after a blister(s) has formed, i.e., 2- 5 days after onset of a cold sore. This is a benefit over docosanol-based products and prescription antiviral medications, which need to be started within 2 days of the onset of a sore, being ineffective once blisters form.

Anti-inflammatory effect

Medium chain fatty acids, such as those found in mothers milk*, and used in Zap-H™, can reduce inflammation by reducing the inflammatory molecules, i.e., cytokines, that target pro-inflammatory immune cells, such as macrophages**. The anti-inflammatory feature of Zap-H™ fatty acids can potentially help reduce the swelling and symptoms of skin sores. Such an anti-inflammatory effect by topical application of fatty acids or oils has not been approved by the FDA.

[*Kainonen, et al; Immunological programming by breast milk creates an anti-inflammatory cytokine milieu in breast-fed infants compared to formula-fed infants. Br J Nutr. 2013 Jun;109(11):1962-70. doi: 10.1017/S0007114512004229.
**Yu, et al; Medium Chain Triglyceride (MCT) Oil Affects the Immunophenotype via Reprogramming of Mitochondrial Respiration in Murine Macrophages. Foods. 2019 Nov 5;8(11):553. doi: 10.3390/foods8110553]

Zap-H™ & Biofilm

An additional benefit for Zap-H™ pertains to biofilm. Biofilm is a complex extracellular matrix that is formed by microorganisms, which protects them from substances in their local micro-environment, and this includes antibiotics, antiviral agents, and some antiseptic agents. Viruses are known to “hide” within bacterial biofilm, and in this way, they are protected from the immune system and topical formulations.

Plant oil fatty acids, in addition to having viral-membrane disrupting properties, have also been shown to have microbial membrane disrupting effects against numerous pathogenic bacteria. Moreover, fatty acids are also known to have biofilm disrupting effects against numerous bacteria. Biofilm protects both bacteria, and any viruses hidden within such biofilm. With respect to viral particles embedded in biofilm, biofilm disruption would be beneficial as a manner by which to expose such hidden virions, making them more susceptible to treatment strategies.

Biofilm is a protective structure produced by microorganisms and is difficult to break down. Detergents have commonly been used to break down biofilms. Detergents comprise molecules called surfactants which reduce surface tension and penetrate the protective biofilm matrix, effectively dispersing organic material and weakening structural bonds. Furthermore, detergents have been combined with enzymes (proteases, amylases) and are shown to be highly effective disinfectants, removing a high number and concentration of microorganisms.

Zap-H ™ cream was initially developed as a “bio-detergent”, a bacterial biofilm disrupting technology, before it was found to have viral membrane dissolving properties. The blend of Zap-H™ ingredients has been shown to destabilize biofilm in multiple types of microbes. In-vitro lab testing at an independent top microbiology testing center demonstrates effects against mature biofilm organisms, including Gram positive Staph. aureus and Enterococcus; Gram negative Pseudomonas a., E. coli, and Klebsiella p.; and Candida fungal biofilm.

Zap-H ™ breaks down biofilm in the same manner as it breaks down viral envelopes, i.e., a bio-detergent like action - it physically interacts with structural molecules, leading to structural instability and biofilm breakdown. Furthermore, because viruses reside, i.e., "hide", within biofilm structure, if the surrounding biofilm is disrupted then it exposes the virus particles. The viral particles, virions, can then be targeted and have their envelopes dissolved by a detergent like compound, such as Zap-H™. In summary, Zap-H ™ acts as a "bio-detergent" that disrupts biofilms, exposing hidden viral particles, which can then be targeted by such membrane disrupting compounds. Such a biofilm disrupting mechanism has not been proven by the FDA.

When open sores develop, bacteria infiltrate such open wounds, and form biofilm as a manner by which to protect themselves. Bacteria are known to reside within biofilm in the eschar (i.e., scab) above a wound bed, such as a scabbed cold sore lesion. Viruses are known to lodge within bacterial and fungal biofilms. In this respect, after a cold sore blister breaks and the scab forms the herpesvirus can exist in the bacterial biofilm of the cold sore eschar. Because Zap-H™ disrupts biofilm, this is yet an additional benefit as it can target viruses that may be present within biofilm located on open sores. Moreover, if one could breakdown biofilm (e.g., with a bio-detergent like Zap-H™), it would expose the encased viral particles, rendering them susceptible to topical viral envelope-disrupting agents, such as Zap-H™, and possibly also the body's immune system. In other words, Zap-H™ does both – it first disrupts the biofilm on skin sores to expose the viral particles within and subsequently dissolves the viral membranes leading to loss of function and their ability to spread. This is correlated wherein Zap-H™ application onto sores that were 5 days old from symptom onset still showed some benefit. Moreover, at this stage the sore has typically progressed to an eschar (i.e., scab). Nonetheless, subjects reported that their symptoms were resolved more quickly with Zap-H™ application than without it, even at this relatively late stage of application, as compared to a scabbed sore that was left alone. Again, this has not been proven by the FDA.

Zap-H™ & Skin Absorption

A yet additional benefit for Zap-H™ is rapid skin absorption. Moreover, when a virus targeting formulation is applied topically, in order for it to be effective, it needs to penetrate into the skin such that the ingredients can actually reach the viral particles which are buried under the skin, and potentially within biofilm. Zap-H™ ingredients

comprise a water-based formulation which has rapid skin penetration, and this enhances its beneficial effects on skin sores (i.e.., the active ingredients can actually reach and make contact with the viral particles). A further benefit is that a formulation that absorbs well does not leave a visible or irritating residue on the skin/ lip.

When we tested numerous over-the-counter (OTC) products, it was noted that most did not have good skin absorption properties. Docosanol, for example, has shown poor skin permeation properties. In fact, the Product Monograph from a pharmaceutical company, the manufacturer/ distributor of a docosanol 10% cream, on November 26, 2013, specifically states: [“Dermal and gastrointestinal absorption of docosanol is limited…”] Again, these are not our words, these are stated by the product manufacturer. If a composition does not absorb through the skin, then one can imagine that there is limited ability for such a product to target a virus that is lodged deep underneath the skin surface. Zap-H™, on the other hand, absorbs quickly, typically within10 minutes. This is due to the water-based emulsion of the Zap-H™ formula. Such rapid penetration through the skin and into the local tissues allows for the ingredients to reach the cells. Any viral particles that are either ready to enter a host cell, or those newly formed viral particles that have exited the cells can be targeted by the absorbed Zap-H™, which will dissolve into the viral envelope, impeding viral function and ability to spread.

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GENITAL HERPES

The genital herpesvirus (HSV2) is structurally very similar to the cold sore HSV1 virus particle. The viral envelopes are similar, as both are formed from the host cell wall. In this respect, because Zap-H™ targets the viral envelope by a detergent like physical interaction, it theoretically would have effectiveness against the genital HSV2 viral envelope as it does against HSV1. Clinical testing for genital herpes has not yet been performed, and as such, we are not able to give any data pertaining to Zap-H™ for use on HSV2 genital herpes sores. However, due to the similarities of HSV2 to HSV1 viral envelopes, and the safety or the ingredients it is thought that targeting HSV2 genital sores is within the realm of possibility to be effective. The information provided herein is for healthcare professionals.

SHINGLES

Shingles rash is the reactivation of the chicken pox herpesvirus (Varicella Zoster, or Herpes Zoster - HZ) infection in adults. It can be very painful and debilitating. Zap-H™ has not been formally tested for shingles, however, because shingles is caused by a similar herpesvirus, with a similar viral envelope, anecdotal reports by 2 individuals indicate that it has been effective in relieving pain symptoms and reducing duration of the shingles rash. Because no formal testing has been done for shingles, at this time we are not able to give any statistical data pertaining to Zap-H™ for use on the shingles rash. However, due to the similarities of HZ to HSV1 viral envelopes, and the safety or the ingredients it is thought that targeting the HZ shingles rash is within the realm of possibility to be effective. This information is provided for healthcare professionals.

CLINICAL EXAMPLES SHINGLES RASH.

2 anecdotal case studies

NOTE: The following are only 2 examples, and it does not prove that Zap-H™ will have similar results for other subjects. (These are the only 2 individuals with shingles to have used Zap-H™.) We show these to highlight that Zap-H™ has a unique ability to potentially resolve a shingles skin rash and symptoms more rapidly than leaving them alone. The shingles rash can last for several weeks, and our limited experience shows significantly more rapid resolution of symptoms and the rash by days or even weeks, compared to no treatment. As for lip sores, any potential benefits for shingles would only occur with early application in the first few days of the onset of the rash.

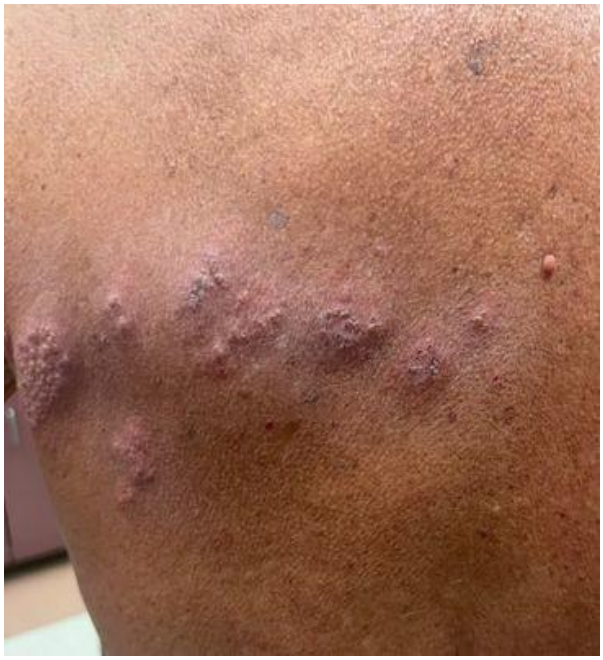
Zap-H™ does not cure any disease and has not been tested or approved by the FDA for use in targeting symptoms associated with a shingles outbreak. This information is provided for healthcare professionals.

CASE #1

PHOTO -1
70 year old, healthy male, unvaccinated for shingles. Day 4 of shingles outbreak. Symptoms of pain, itch and tingling. Diagnosis was made by primary medical physician.

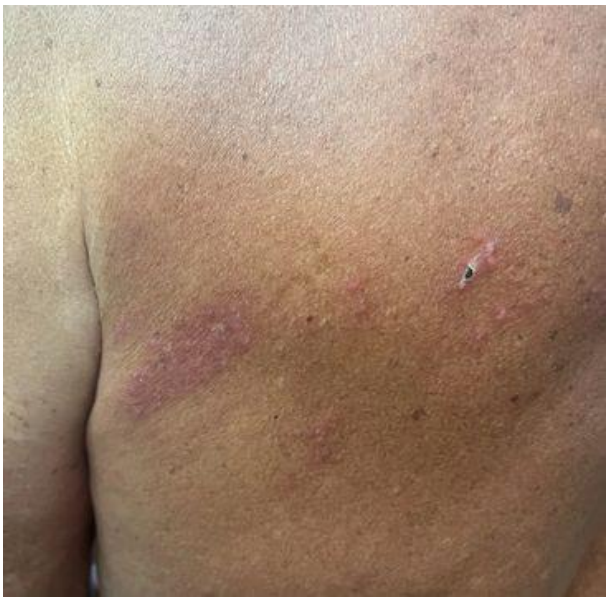
PHOTO - 2
Day 7, after applying Zap-H™ on Day 4, 5 and 6. Painful symptoms were relieved more rapidly, i.e., within a few days, rather than the typical duration of 3-5 week.

PHOTO - 1



SHINGLES (CASE STUDY) BEFORE ZAP-H™ - 4 day old rash

PHOTO - 2



SHINGLES (CASE STUDY) AFTER ZAP-H™ - 3-4 days of application

CASE #2

A 35 y.o. female has had a shingles rash develop on the left side of her cheek numerous times over many years. She had irradiation therapy on her neck years ago, which may have predisposed this area for the shingles rash. With her latest outbreak, after 2 days of the rash, she began applying Zap-H™ cream. The annoying pain subsided within 1-2 days, and the rash began to dry and scab over by the second day. Overall, she stated that the symptoms and rash both subsided much more rapidly, i.e., within 1-2 days, whereas otherwise the pain and symptoms typically lasted for at least a week and longer.