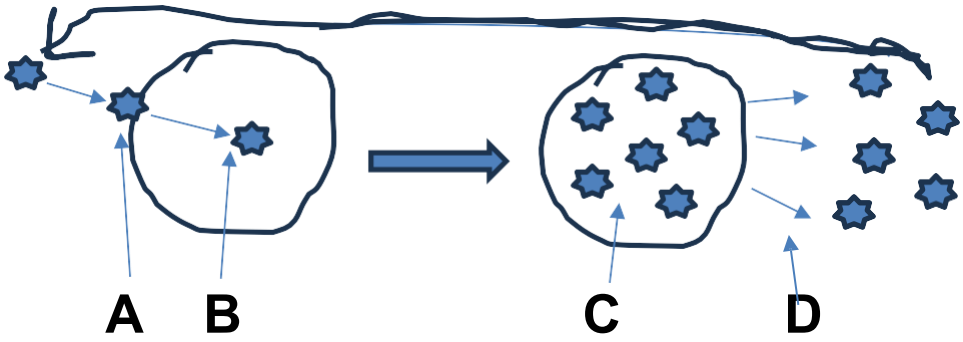
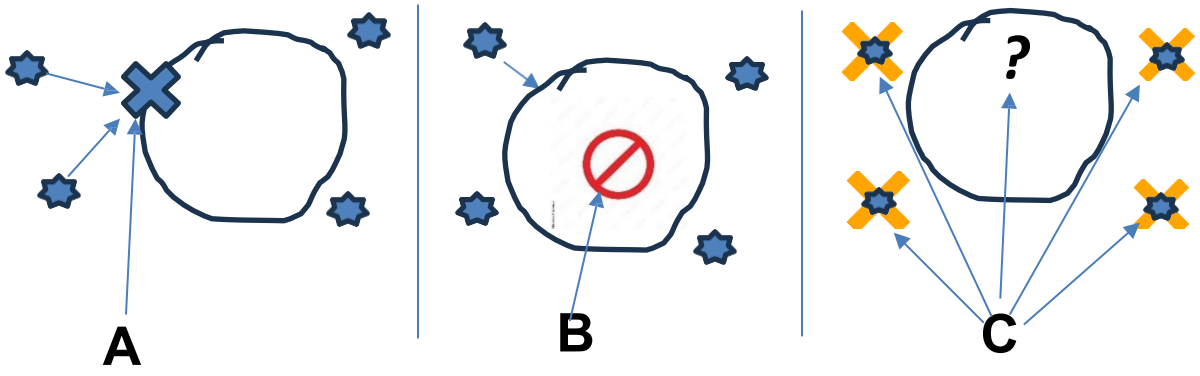
FOR THE HEALTHCARE PROFESSIONAL

Stages of Viral Infection



A- Viral Fusion to cell membrane
B- Viral Entry into cell
C- Viral Replication (intracellular)
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 ((possible intracellular)- disrupts viral membrane

→ 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 results 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 treatments have limited effectiveness.

In addition to having developed methods by which to hide itself from the immune system, HSV1 infection therapies have had limited success for one main reason - current treatment methods do not target the virus directly. For example, many cold sore treatments focus on relieving the symptoms, namely itch, tingling and pain, wherein the effects are typically of temporary nature. Second, treatments are available that block viral entry into host cells, however there is no direct effect on HSV1, and the virions can survive. Third, treatments are available that prevent viral replication, but again the virions can survive; hence they can spread. A common denominator for all these treatment 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 treatments 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 treatment strategies. 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 treatment results are best if it is started within 24 hours but 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

Mechanism of action and what it means?

Combining the information from our lab studies and existing publications, it is thought that the key mechanism of action for Zap-H™ is the ability of its ingredients to disrupt the protective viral 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.

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. Disrupting the viral envelope by Zap-H™ can secondarily 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 *. 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 clinical studies with rapid disappearance of cold sores coincides with rapid viral envelope disruption that occurs in the laboratory setting. Zap-H™ comprises such fatty acids that disrupt viral envelopes. This is not a drug effect, rather a "detergent-like" effect 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.]

Further yet, although numerous fatty acids/ oils alone can disrupt viral envelopes, the combination of ingredients in Zap-H™ significantly enhances, i.e., synergizes, such viral envelope disruption. In this way, the combination of Zap-H™ ingredients is profoundly more effective than using such fatty acids/ oils alone.

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 acid oils in combination with enhancing ingredients, rather than the use of synthetic compounds, for the physical disruption of the viral envelope. 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 the dissolution 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.

Our laboratory studies demonstrate that the combination of ingredients in Zap-H™ is more effective for viral envelope disruption than any ingredient used alone. Hospital clinical testing in human subjects was consistent with laboratory testing - combination of ingredients in Zap-H™ was more effective than using any ingredient alone.

While laboratory studies show viral envelope disruption by fatty acids, an associated clinical effect has not been evaluated by the FDA. However, the rapid in-vitro viral envelope disruption correlates with a rapid in-vivo effect (i.e. demonstrated by a double-blind, hospital clinical study showing a significant reduction in time for sores to resolve with the use of Zap-H™). In other words, the clinical use of Zap-H™ correlates highly with results obtained in laboratory testing (both our results and prior published results).

Effective even at 5 days post onset of symptoms

Our clinical experience further shows that individuals using Zap-H™ anecdotally note that it is effective even if treatment 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 cold sore, being ineffective once blisters form.

Generalized Antiviral Effect

Zap-H™ has also shown effects against numerous other viruses that were tested in the lab. These pertain not only to herpesvirus, but also coronavirus, RSV (respiratory syncytial virus), influenza and Mpox viruses. The formulations need to be altered for specific viruses for best results - i.e., the same formula is not optimal for every virus. We do not advocate for the Zap-H™ formulation to be used to mitigate symptoms for these other viruses, but the lab results further confirm the general viral targeting features of **Zap-H™ ingredients.**

Anti-inflammatory effect

Fatty acids can reduce inflammation in epithelial cells, as for example those lining the mammary glands. An anti-inflammatory feature of fatty acids in Zap-H™ can help reduce the swelling and symptoms of cold sores.

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 treatment strategies.

Plant oil fatty acids, in addition to having viral-membrane disrupting properties, have also been shown to have antimicrobial membrane disrupting effects against numerous pathogenic bacteria. Moreover, fatty acids are 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 an antibacterial biofilm disrupting technology, before it was found to have viral membrane disrupting properties. The blend of Zap-H™ ingredients breaks down biofilm in multiple types of microorganisms. 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 or approved 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 (such as with 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 cold 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 clinically by individuals where treatment of cold sores with Zap-H™ was started up to 5 days from symptom onset. At this stage the outbreak formed 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 in treatments, as compared to an untreated cold sore scabbed lesion.

Zap-H™ & Skin Absorption

A yet additional benefit for Zap-H™ is rapid skin absorption. Moreover, when an antiviral formulation is applied topically, in order for it to be effective, it needs to penetrate into the skin such that the active 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 clinical efficacy (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, which is lodged deep underneath the skin surface. Zap-H™, on the other hand, absorbs quickly, typically within10 minutes. This is due to the presence of skin permeation enhancers in 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 disrupt 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. (Clinical testing for genital herpes has not yet been performed.) At this time, we are not able to recommend Zap-H™ for use on HSV2 or genital herpes sores. 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 (see below) indicate that it may be effective in relieving pain symptoms of the shingles rash and reducing duration of the rash. Because no formal testing has been done for shingles, at this time we cannot recommend the use of Zap-H™ for application on shingles sores. This information is provided for healthcare professionals.

[Show Less]

CLINICAL EXAMPLE PERTAINING SHINGLES RASH.

PHOTO #1
68 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 than the typical duration of 3-5 weeks.

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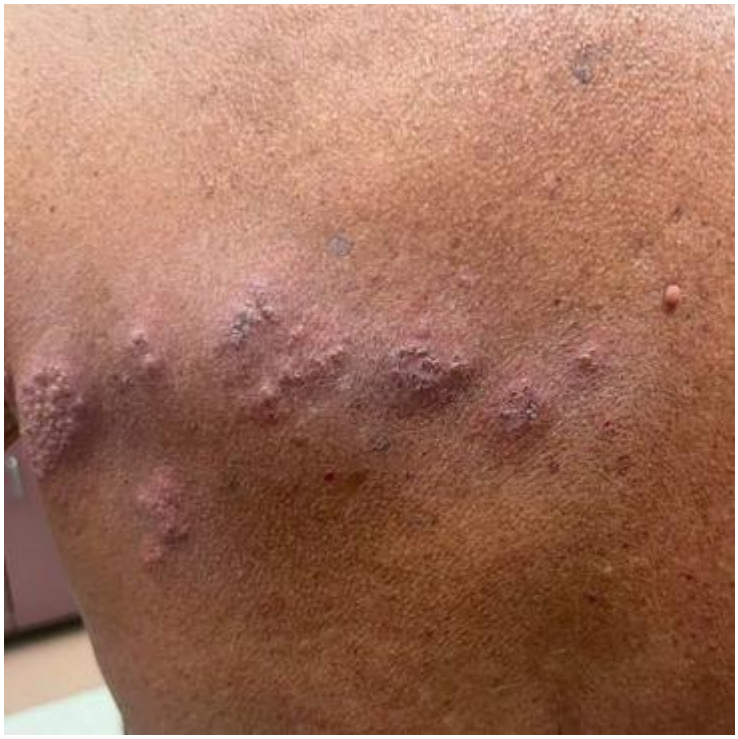
Note. This is only one example, and it does not prove that Zap-H™ will have similar results for other subjects. We show this to highlight that Zap-H™ ingredients have a unique ability to potentially resolve a viral skin infection more rapidly. The shingles rash can last for several weeks. As for HSV1 cold sores, any benefits for shingles would only occur with early application in the first few days of the onset of the rash.

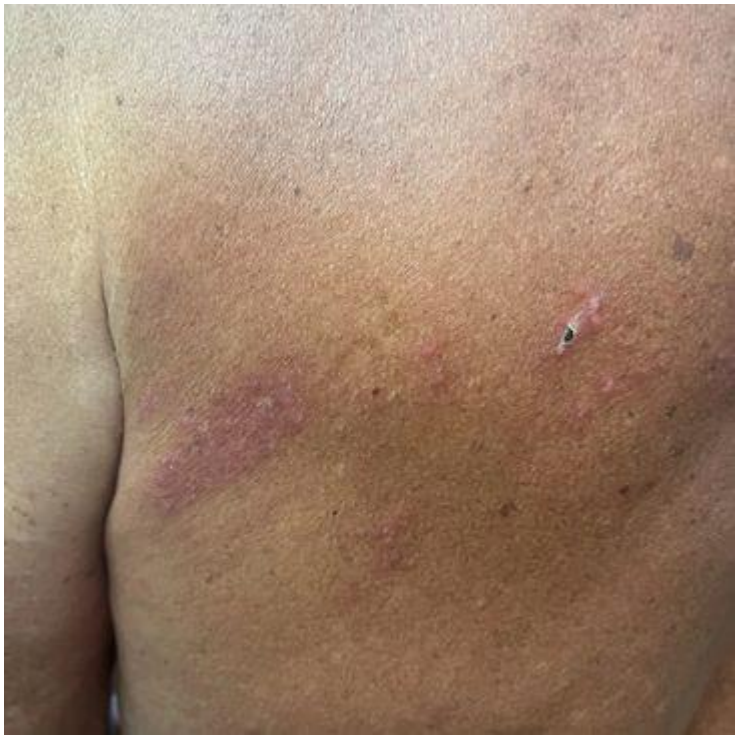
Zap-H™ does not cure any disease and has not been tested or approved by the FDA for use in targeting symptoms associated with a shingles outbreak. This information is provided for healthcare professionals.

#1



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

#2



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