Sexually Transmitted Diseases:
AN ILLUSTRATED GUIDE TO DIFFERENTIAL DIAGNOSIS

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Sexually Transmitted Diseases: An illustrated guide to differential diagnosis is provided as an educational service by Burroughs Wellcome Co., Research Triangle Park, NC.

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Since the beginning of recorded history, the diagnosis and management of sexually transmitted disease (STD) have challenged the physician's art. The recent increase in the incidence of genital herpes may make it appear to be a disease of modern times, but writings that date back to Hippocrates and Byzantine physicians include descriptions of clinical signs that sound remarkably like genital herpes.

In the past, the method of diagnosis by inspection and patient history was impeded by anthropological, religious, and societal attitudes. Social mores and misconceptions frequently made patient management less than ideal. Today's clinician practices on more solid ground, but the differential diagnosis of genital herpes can still be problematic. While clinical manifestations are primary clues, not every patient with genital herpes will present with classic signs and symptoms.

This guidebook narrows the range of diagnostic possibilities and helps the clinician maximize available information—patient history, clinical findings, and laboratory test results—to differentiate genital herpes from other diseases with similar clinical presentations. Also included are guidelines for appropriate use of ZOVIRAX® (acyclovir) Capsules. In selected patients, ZOVIRAX provides effective therapy and suppression of genital herpes infection.
SEXUALLY TRANSMITTED
DISEASES WITH MUCOCUTANEOUS
MANIFESTATIONS

Herpes simplex virus is the most frequent cause of genital ulcers in the United States.\(^1\) However, other sexually transmitted diseases (STDs) may produce lesions that resemble genital herpes. While each STD has specific clinical characteristics, overlapping of signs and symptoms does occur. In fact, it has been found that even among venereologists, clinical impressions of genital herpes ulcers are in error almost 40% of the time.\(^2\)

Nevertheless, visual impressions are an important first step toward differential diagnosis. The following chart presents key distinguishing characteristics of five STDs that produce genital lesions.

<table>
<thead>
<tr>
<th>Characteristics of Genital Ulcers in Sexually Transmitted Diseases</th>
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<tbody>
<tr>
<td><strong>Herpes</strong></td>
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<tr>
<td>Primary lesions</td>
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<tr>
<td>Number of lesions</td>
</tr>
<tr>
<td>Border</td>
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<tr>
<td>Depth</td>
</tr>
<tr>
<td>Base</td>
</tr>
<tr>
<td>Secretion</td>
</tr>
<tr>
<td>Induration</td>
</tr>
<tr>
<td>Pain</td>
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<tr>
<td>Lymph nodes</td>
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Adapted from Kraus SJ.*

*Useful in differential diagnosis.
Because there is considerable overlap in the clinical manifestations of genital herpes and those of other ulcer-producing STDs, the following flow-chart may be of use to the clinician for differential diagnosis.

Diagnostic Flow Chart for Differentiation of Genital Herpes from other STDS

SEXUALLY ACTIVE PATIENT WITH GENITAL ULCER(S)

Yes

Vesicle Present

No

Darkfield Examination

Negative

Positive

Nonvenereal serological test for syphilis (FTA-Abs, VDRL, etc.)

Negative

Positive

Probable Syphilis

Obtain confirmatory FTA-Abs or MHA-TP

Negative

Yes

Probable Herpes

No

History and Exam Suggest Herpes

1. History of vesicles
2. History of recurrences
3. Exposure to herpes
4. Painful, superficial lesions

Clinical characteristics of ulcer (and lymphadenopathy, if present)

Painful, superficial, recent (tender firm nodes: no erythema)

Positive

Possible Herpes or Chancre
Obtain virologic confirmation of HSV

Negative

Possible Chancre
Obtain culture for H. ducreyi

Positive

Chancre

Reconsider all diagnoses, including LGV, chancre, scabies, fixed drug eruption, trauma, pyoderma. If ulcer(s) chronic, consider biopsy for Donovanosis, malignancy. Consider trial of antimicrobial therapy. Repeat serological tests for syphilis. If lesion(s) resolve and then recur, reassess for herpes.

Negative

Painless, indurated (firm nodes, non- or minimally tender)

Possible Syphilis

Repeat darkfield examination and serological tests for syphilis

Negative

FTA-Abs = fluorescent treponemal antibody-absorption, MHA-TP = microhemagglutination assay for Treponema pallidum.

*Adapted from Kraus SJ.*
Because genital herpes does not have to be reported, we have little accurate data on national incidence. In Seattle, an STD clinic recently reported over a doubling of the incidence over a five-year period. Information from the Centers for Disease Control (CDC) showed as much as a 90% increase in patient visits to private practitioners in the United States for genital herpes. These figures reflect both an increased recognition and an increased incidence of genital herpes.

First episodes of genital herpes are frequently more severe and may be associated with systemic symptoms, multiple genital and extragenital sites, and prolonged duration of viral shedding and lesions. Patients with clinical or serologic evidence of prior herpes simplex virus (HSV) infection often have a milder illness than those with a true primary infection. Whether the primary infection is due to HSV-1 or HSV-2, the clinical picture appears similar.

In contrast to clinical signs and symptoms of primary genital infections, recurrent infections are localized to the initial site, usually the genital region. While there is considerable variation in severity and duration, the symptoms of recurrent genital herpes are often mild, and external genital lesions are unilateral.

A primary genital herpes infection usually begins with an erythematous rash that develops into a cluster of grouped vesicles on a red base. Regional lymphadenopathy and systemic symptoms usually accompany the vesicles. The typical primary infection runs a 3- to 4-week course.

In recurrent herpes, approximately 50% of patients experience a prodromal phase—from a mild, tingling sensation one-half hour to 48 hours prior to eruption, to shooting pains in the buttocks, legs, or hips one to five days before the eruption. Recurrent genital herpes is usually less florid than the primary episode; the vesicles are mild to moderately painful, and lymphadenopathy is rare.

The intact vesicle is the strongest clinical indication of genital herpes. Too often, by the time a patient seeks treatment, the vesicles have been ruptured and the site has ulcerated. At this point, differential diagnosis must be based on a combination of clinical manifestations, patient history, and laboratory tests.
Unruptured vesicles of herpes simplex in vulvar area

Irritated herpes simplex on the buttocks

Recurrent herpes simplex at root of penis, history of recurrences after intercourse

Herpes simplex lesions of female genitalia

While infrequent in uncomplicated herpes, scarring may occur secondary to bacterial infection
SYPHILIS

It has been said that, "He who knows syphilis knows medicine." This adage, referring to the protean manifestations of syphilis, still holds true—with the incidence of misdiagnosis as high as 40%.6

The classic chancre is a single, painless, usually eroded papule at the inoculation site. The chancre, often an ulcer with a firm, indurated, cardboard-like base, may appear after an average 21-day incubation period (range: 3 to 90 days),7 and usually heals within 3 to 6 weeks (range: 1 to 12 weeks). Healing is usually complete or leaves a thin atrophic scar.7 In addition to the external genitalia, chancres may occur on the cervix, mouth, perineal area, anal canal, or breast.

Clinical manifestations of secondary syphilis are diverse, but skin lesions occur in approximately 90% of cases.7 The lesions may be macular, papular, maculopapular, pustular or some variation, but never vesicular.7

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<td>Herpes</td>
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<td>Appearance of primary lesions</td>
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<tr>
<td>Induration</td>
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<tr>
<td>Pain</td>
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<tr>
<td>Lymph nodes</td>
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Primary syphilitic chancre at the inoculation site

Primary syphilitic chancre on glans penis

Primary syphilitic chancre on penile shaft

Infectious papular lesions of secondary syphilis on palms
Chancroid (soft chancre) is a much less frequent cause of genital ulcers than herpes simplex virus or syphilis. It is caused by Hemophilus ducreyi and has been considered an STD of the lower socioeconomic groups. There is a higher incidence of chancroid in nonwhites, and males appear to have a higher incidence than females. Due to the low incidence of chancroid in the United States, the presence of painful, multiple ulcers may lead the clinician to suspect genital herpes. If the patient’s history reveals recent travel to southeast Asia, Africa, South America, Central America, or the southeastern United States, and if clinical features of chancroid are present, the diagnostic possibilities are narrowed.

Genital ulcers generally develop within one week of contracting chancroid, and infection spreads to regional lymph nodes with subsequent breakdown and discharge of pus. Unlike syphilis, chancroid more often causes multiple ulcers than solitary lesions. Laboratory diagnosis is difficult and clinicians should check with a microbiology laboratory about special isolation procedures.

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<th>Clues to Differential Diagnosis⁸</th>
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<tbody>
<tr>
<td>Differences</td>
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<tr>
<td>---</td>
</tr>
<tr>
<td>Herpes</td>
</tr>
<tr>
<td>Chancroid</td>
</tr>
<tr>
<td>Appearance of primary lesions</td>
</tr>
<tr>
<td>Grouped vesicles on a red base; crusts form as lesions dry up, producing erosion, ulcerations, and possible scarring</td>
</tr>
<tr>
<td>Induration</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>Pain</td>
</tr>
<tr>
<td>Firm</td>
</tr>
<tr>
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LGV is often confused with other STDs: it has the lymphadenopathy of syphilis and genital herpes and the buboes of chancroid. Like chancroid, LGV should be suspected if there has been recent travel to southeast Asia, Africa, South America, or the southeastern United States. LGV is caused by \textit{Chlamydia trachomatis} and the primary lesion, often ignored, is a painless, inconspicuous vesicle or vesicopapule. The secondary stage, more critical to differential diagnosis, is characterized by an inguinal syndrome (acute lymphadenitis with buboes) and/or anogenital syndrome (acute hemorrhagic proctitis). The patient may also present with fever, chills, headache, or malaise. The delayed onset of regional adenopathy — 1 to 2 weeks after the primary lesion has subsided with subsequent suppuration — is an important clue to differential diagnosis.

<table>
<thead>
<tr>
<th>Clues to Differential Diagnosis*</th>
<th>Differences</th>
<th>Similarities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Herpes</td>
<td>LGV</td>
</tr>
<tr>
<td>Appearance of primary lesions</td>
<td>Grouped vesicles on a red base; crusted as lesions dry up, producing erosions, ulcerations, and possible scarring</td>
<td>Usually one papule, ulcer, or vesicle with variable border, base and secretion</td>
</tr>
<tr>
<td>Induration</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Pain</td>
<td>Common</td>
<td>Variable</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>Firm</td>
<td>Secondary stage shows inflamed, tender, may suppurate; delayed onset after healing of primary lesion</td>
</tr>
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A characteristic unilateral, inguinal bubo of second stage lymphogranuloma venereum (inguinal syndrome)

LGV: large, single necrotic ulcer of scrotum, note hyperpigmentation at margin of ulcer indicating chronic inflammation

LGV with scrotal lymphedema, note partial loss of pigmentation and peripheral follicular hyperpigmentation, indicating chronicity of infection
The causative organism of GI is *Calymmatobacterium granulomatis*, a gram-negative bacterium with a distinctively large capsule and a bulge of chromatin (the Donovan body) at one end, giving it the look of a closed safety pin under the microscope. GI is rare in the United States (fewer than 100 cases annually), but very common in New Guinea, India, Central Australia, the Caribbean, and many other tropical or subtropical environments.11

The primary lesion begins as an indurated nodule that erodes to form a beefy, granulomatous raised ulcer. As the lesion progresses slowly, it may form a series of adjoining lesions. Eventually these lesions may eat into skin and underlying tissues, including bone, without causing significant lymphadenitis. The subcutaneous extension of the ulcerative process may produce a pseudo-adenopathy.9

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Characteristic ulcerations of granuloma inguinale in the vulvar area with edema of the labia.

The prepuce or glans penis is the most common site of granuloma inguinale in the male.

Granuloma inguinale: deeply punched-out ulcer with jagged edges involving the glans penis; ulcers bleed readily on contact.

Two large eroded ulcers on dorsum of glans penis, note firm, elevated, rolled borders.
Molluscum contagiosum is caused by a poxvirus and characterized by multiple, pearly, smooth, waxy umbilicated papules. Once a disease seen mostly in children, it has become an increasingly prevalent STD, although investigators have been unable to propagate the virus in the laboratory setting. Molluscum contagiosum has been associated with other STDs in as many as 67% of cases. Auto-inoculation is common and may be reflected in the clinical appearance of multiple lesions in a linear pattern along the site of a scratch (pseudo-Koebner phenomenon). If left untreated, the disease may persist, producing giant lesions the size of a dime.

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<td>Grouped vesicles on a red base; crusts form as lesions dry up, producing erosions, ulcerations, and possible scarring</td>
</tr>
<tr>
<td>If a molluscum papule becomes irritated, red, and ulcerated, it may mimic genital herpes. Smooth, pearly papules of molluscum reflect light and may appear similar to the vesicles of genital herpes.</td>
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<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>None</th>
<th>–</th>
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<tbody>
<tr>
<td>Induration</td>
<td>None</td>
<td>None</td>
<td>–</td>
</tr>
<tr>
<td>Pain</td>
<td>Common</td>
<td>Rare, unless irritated</td>
<td>–</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>Tender, firm</td>
<td>Nontender</td>
<td>–</td>
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Scabies is an ancient disease, reputedly rampant among Napoleon Bonaparte's troops. A tiny mite, *Sarcoptes scabiei*, is the causative organism. The fertilized female burrows into the stratum corneum of the human host and lays her eggs. Nocturnal itching is the main clinical complaint and is probably an allergic reaction to the mite's feces. Typical clinical manifestations are red, edematous, and often excoriated papules on finger webs, elbows, buttocks, penis, and scrotum. Diagnosis is often supported by a similar history of itching among close contacts. Scabies is a great imitator and may be confused with a variety of pruritic dermatoses. In some cases, generalized urticaria may be the only presenting symptom. Diagnosis can be confirmed by microscopic evidence of the parasite in skin scrapings taken near a burrow or by skin biopsy.

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<tr>
<td>Urticaria/Pain</td>
</tr>
<tr>
<td>Pain is common with genital herpes</td>
</tr>
<tr>
<td>Mode of Transmission</td>
</tr>
<tr>
<td>Most frequently, through close contact with a person who is shedding virus</td>
</tr>
</tbody>
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Scabies frequently coexists with other STDs including genital warts.

Scabies infections can be transmitted nonsexually between close family members, eg, this prepubertal boy.
Genital warts are known by many different names: fig warts, venereal warts, and condyloma acuminata. In the late fifteenth century, anogenital warts were frequently confused with the typical warts of secondary syphilis, condyloma lata. The old-fashioned term “gonorrheal warts” is a reminder that genital warts frequently occur with other STDs, and patients with genital warts should be routinely examined for other STDs. Genital warts must also be differentiated from genital lesions, particularly those of condyloma lata in secondary syphilis and malignant conditions of the anogenital area.

Genital warts may be transmitted by direct or indirect contact and autoinoculation. The typical condyloma acuminata is a fleshy, nonhorny wart most commonly seen on the genitalia, mouth, or perianal area. In the male, warts often appear on the frenulum, the coronal sulcus, and terminal urethra; however, any part of the penis or scrotum may be affected. In women, the vulva, perineum, and anus are the most common sites.

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In severe cases of perivaginal warts, genital herpes or other STDs may also be present.

Prominent glands around the head of the penis mimic warts or tiny vesicles of genital herpes.

In the moist perineal area, a wart may lose the typical rough verrucous surface.

Oral warts may appear as a result of oral-genital contact.

Warts near the urethral meatus are kept moist and are often firm, red, smooth, and bleed easily.
In daily practice, the clinician may see a wide variety of genital lesions that either mimic, or are suggestive of, genital herpes. Familiarity with the skin manifestations, including other STDs, nonvenereal diseases, allergic dermatoses, trauma, and fixed drug eruptions will facilitate the differential diagnosis of genital herpes. The following photographs illustrate the diversity of presentations the clinician may observe in the differential diagnosis of genital herpes.

**Yeast infections**
*Candida albicans* occurs most commonly in the skin folds of the obese and in uncircumcised men with tight foreskins. Satellite pustules and skin cultures help confirm the clinical diagnosis.

**Seborheic dermatitis**
A very common papulosquamous skin disease; look for other commonly affected areas such as nasolabial folds on the face and midanterior chest.
**Trauma, continued**
Superficial ulceration of penile shaft secondary to trauma

**Ecchymosis and hyperpigmentation secondary to trauma**

**Lichen planus**
An infection of the penis showing typical red, elevated lesions and central white Wickham’s striae. Lesions may ulcerate and atrophy. Differentiate from genital herpes with Tzanck smear and examine oral buccal membrane for lacy white lesions of lichen planus.

**Bacterial folliculitis**
When observed in the pubic area, *grouped pustules* should not be confused with the grouped vesicles of genital herpes.

**Trauma**
Erosion on penile shaft secondary to oral sex.

**Purpura secondary to intercourse**

**Ecchymosis secondary to oral sex**
OTHER GENITAL LESIONS, CONTINUED

**Fixed drug reaction**
May involve the glans penis, usually occurs repeatedly in one location after ingesting the allergenic drug. Typical genital lesion is a well-delineated, edematous red plaque that may evolve into a blister or ulcer. Drugs most frequently implicated are phenolphthalein, barbiturates, and antibiotics.

**Erythema multiforme**
A common reaction secondary to herpes simplex virus infections. The clinician may see classic target lesions on the extremities, particularly the hands.

**Classic target lesions on the hand**

**Allergic contact dermatitis**
A variety of irritants or allergens, including condoms, may produce vesicles with edema and/or erythema; patient history helps confirm diagnosis.

**Balanitis cincta sicca of Reiter's syndrome**
A patch of erythema with a shiny, smooth, moist surface is localized on the glans penis or inner surface of the foreskin in males and on the inner surface of labia majora or minora in females.

**Lice**
If hemorrhagic vesicles are observed on the glans penis, check for individual insects in pubic area.
Balanitis circumscripta

Atrphy secondary to chronic use of topical steroids
Topical steroid creams should never be given to patients with herpes simplex and should be used with extreme caution on the penis, vagina, or perineum where thin epithelial tissue can easily atrophy.

Psoriasis
Psoriasis may mimic genital herpes with papules and apparent lack of scales.

Bowenoid papulosis
Viral induced anogenital lesions mimicking warts or herpes simplex lesions, but having potential for malignant degeneration.
A number of test methods have been developed to reduce cost and shorten the time to differential diagnosis of the herpes simplex virus. Highly accurate cell cultures, however, still require several days for results. Although less accurate than cell culture, the Tzanck smear is a quick, easy, and valuable confirmatory test. In the Tzanck test, cells scraped from the base of the lesion are stained (Giemsa or Wright’s) and examined for the presence of multinucleate giant cells. Definitive diagnosis can also be made with a simple excisional biopsy.

**Tips for handling viral specimens**

The timing of collection is critical for smears of cells and cultures of herpes simplex virus (HSV). As time increases from the onset of the disease, the number of positive results decreases, because viral shedding decreases with time. Vesicles will give a higher yield than ulcers, and the drier the ulcer, the less likely to yield viable virus.

If the specimen is to be transported, it should be kept at 4°C (or on ice). It will remain viable in an appropriate transport medium for 48 to 96 hours at this temperature, although a slight loss of titer occurs over time. HSV is viable for years if stored at −70°C. Since herpesviruses are inactivated at −20°C, a specimen for culture should never be frozen in an ordinary freezer. Slides to be examined for the presence of giant multinucleate cells should be air-dried and fixed with 95% methanol.

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**How to do a Tzanck test**

- Rupture an intact vesicle with a scalpel blade, and blot the fluid with a gauze square.
- Gently scrape base of lesion to remove cells — try to minimize or prevent bleeding.
- Smear material onto a slide with the blade.
- Air-dry, then fix the specimen with 95% methanol.
- Apply Giemsa or Wright’s stain or methylene blue for 3 minutes.
- Observe the preparation under low and high power for characteristic multinucleate giant cells. Remember chicken pox and herpes zoster also produce multinucleate giant cells.

**What to look for in the Tzanck smear**

Some microbiologists believe that only multinucleate giant cells showing margination of the nucleoplasm — nuclei with darker blue rims and centers of lighter blue (steel-gray nuclei) — should be called true positives. Because aggregates of normal keratinocytes can simulate multinucleation (but lack margination), both types of multinucleate cells may be observed in a Tzanck test slide.

**New diagnostic tests**

- **Immunofluorescence/immunoperoxidase.** Scrapings from the bases of vesicular lesions (or, less successfully, from ulcers) can be stained with specific antibodies and examined using either immunofluorescence or immunoperoxidase techniques. These methodologies yield approximately 80% agreement with culture.

- **Enzyme-linked immunosorbent assays (ELISA).** This important diagnostic technology has recently been developed for HSV antigens. Although somewhat less sensitive than viral culturing, ELISA may offer the advantage of providing more rapid laboratory diagnosis of HSV. Additionally, ELISA testing is associated with a false-positive rate of approximately 2%.
Both margiated and nonmarginated multinucleate giant cells

Marginated multinucleate giant cell

Nonmarginated multinucleate giant cells
MANAGING THE PATIENT WITH GENITAL HERPES

Medical management

An ideal therapy for genital herpes would reduce the severity of initial disease and prevent HSV from establishing latency in the sacral ganglia. However, there is no agent known to prevent latency. Currently, the most viable approach to treatment of recurrences is to reduce their frequency and severity with antiviral therapy.

In initial episodes, the goal is to reduce symptoms. As soon as possible after diagnosis, patients should take ZOVIRAX® (acyclovir) Capsules (200 mg by mouth) five times daily for 10 days. This treatment shortens the median duration of the first episodes, reduces healing time, and rapidly stops viral shedding.24 In rare cases, a patient with an extremely severe episode, or an immunocompromised patient, may require more aggressive management, including hospitalization and therapy with intravenous ZOVIRAX® (acyclovir sodium).

Topical therapy should be aimed at keeping lesions clean and dry using hydrogen peroxide and frequent warm water compresses. This will minimize the risk of secondary bacterial infection. In addition, ZOVIRAX® (acyclovir) Ointment can promote healing of herpes lesions.

When recurrent incidences of genital herpes are problematic, continuous treatment with ZOVIRAX Capsules, 400 mg b.i.d. (or 200 mg PO three to five times per day), has been shown to reduce the frequency of active disease by at least 75%25 in patients with frequent recurrences (≥ six per year24). Long-term therapy of at least 3 years has shown high levels of safety and efficacy.26 The dose of ZOVIRAX should be individualized. Patients who can benefit most from a daily regimen include those with frequent or severe recurrences, as well as those whose emotional well-being is impaired by outbreaks.

Patients with less frequent or severe recurrences may take a 5-day course of therapy: from onset of prodrome, ZOVIRAX Capsules, 200 mg five times a day for 5 days, decreases viral shedding and healing time. The earlier the intervention with ZOVIRAX therapy, the more favorable the clinical results. Self-administration by the patient at first sign of prodrome is most efficacious. Full prescribing information for ZOVIRAX is provided on the last pages of this booklet.

Counseling

Once herpes simplex is diagnosed, the patient may have many questions. It helps to explain the natural history of genital herpes infections. And it is also important to encourage the patient to abstain from sexual contact while lesions are present, even if s/he is taking ZOVIRAX. HSV can be transmitted during asymptomatic periods but the risk of transmission is less than during the active disease state; use of condoms and/or spermicidal jelly or cream can help minimize risk.

Pregnant women with a history of genital herpes are at risk of delivering a baby with gestational herpes and should be monitored closely.
REFERENCES

**ZOVIRAX CAPSULES, ZOVIRAX SUSPENSION (ACYCLOVIR)**

**DESCRIPTION:** Zovirax is a broad-spectrum antiviral agent. Zovirax Capsules and Suspension are formulations for oral administration. Each capsule of Zovirax contains 200 mg of acyclovir, and the oral suspension contains 200 mg of acyclovir per 5 mL. For the treatment of genital herpes, Zovirax capsules may be taken orally or by mouthwash. Zovirax suspension is a liquid preparation for oral administration. Zovirax capsules are administered orally or by intermittent intravenous infusion. Zovirax suspension is administered by mouthwash or as a concentrate. Zovirax capsules and suspension are not recommended for intravenous administration.

**CLINICAL PHARMACOLOGY:**

**Mechanism of Action:** Acyclovir is a synthetic nucleoside analog that inhibits the viral DNA polymerase. Acyclovir is a prodrug that is activated by the viral DNA polymerase to a triphosphate derivative, which becomes incorporated into the viral DNA, leading to chain termination. Acyclovir is also a potent inhibitor of herpes simplex virus (HSV) and varicella-zoster virus (VZV) DNA polymerases.

**Absorption and Distribution:** Acyclovir is rapidly absorbed following oral administration. It is distributed throughout the body, including the central nervous system. Acyclovir is excreted in the urine and feces.

**Pharmacokinetics:** Acyclovir is metabolized in the liver and excreted in the urine. The half-life of acyclovir is approximately 1 hour. The metabolism of acyclovir is dependent on renal function.

**Drug Interactions:** Acyclovir may interact with drugs that are metabolized by the liver or kidney, such as probenecid. Acyclovir may increase the blood levels of probenecid.

**Contraindications:** Acyclovir is contraindicated in patients with a history of hypersensitivity to acyclovir or its components.

**Warnings and Precautions:** Acyclovir may cause neuropsychiatric symptoms, including headache, dizziness, confusion, and seizures. Acyclovir has been associated with an increased risk of birth defects in animal studies. Acyclovir may cause bone marrow suppression and should be used with caution in patients with bone marrow suppression.

**Dosage and Administration:** The recommended dose of acyclovir for the treatment of genital herpes is 200 mg five times a day for 7 days or 400 mg five times a day for 5 days. The recommended dose of acyclovir for the treatment of varicella-zoster virus infections is 800 mg five times a day for 7 days. The recommended dose of acyclovir for the treatment of herpes simplex virus infections in immunocompromised patients is 2000 mg five times a day for 10 days.

**Nursing Considerations:** Nursing considerations for patients receiving acyclovir include monitoring for neuropsychiatric symptoms, monitoring for bone marrow suppression, and monitoring for creatinine levels.

**Patient Counseling:** Patients should be counseled to report any signs of neuropsychiatric symptoms, bone marrow suppression, or creatinine level changes.
neutrophilic leukaemia (NHL) and therefore a malignancy. NHL is a condition characterised by the uncontrolled growth of malignant lymphocytes in the bone marrow, resulting in anemia, platelet dysfunction, and an increased risk of bleeding. NHL can be classified into several subtypes based on their characteristics and clinical behaviour. One of these subtypes is lymphoma, which is a type of NHL characterized by the proliferation of malignant B cells in the lymphatic system. Lymphoma can be further divided into Hodgkin lymphoma and non-Hodgkin lymphoma. Hodgkin lymphoma is a type of lymphoma that affects the lymph nodes, while non-Hodgkin lymphoma can affect various organs and tissues in the body.

In the context of NHL, Rituximab is a monoclonal antibody that targets CD20, a molecule expressed on the surface of B cells. Rituximab is used in the treatment of B-cell NHL to help destroy these cancerous cells, thereby improving the patient's immune response and potentially eliminating the disease. Rituximab is often used in combination with chemotherapy to enhance its efficacy. The combination of Rituximab and chemotherapy can lead to a better response rate and improved survival for patients with NHL.

In summary, the treatment of NHL, including lymphoma, involves a combination of strategies such as chemotherapy, radiation therapy, and the use of monoclonal antibodies like Rituximab. These treatments aim to destroy the malignant B cells and improve the patient's overall health and quality of life. The choice of treatment depends on the specific subtype of NHL and the patient's overall health status. Ongoing research continues to explore new treatment options and improve outcomes for patients with NHL.
**ZOVIRAX® Sterile Powder**

**DESCRIPTION.** Zovirax is the brand name for acyclovir, an antiviral drug used to treat several viral infections. Zovirax® Sterile Powder is a formulation for intravenous administration. Each 1g of sterile powder contains 1g of acyclovir, equivalent to 1g of acyclovir base. The inactive ingredients in Zovirax® Sterile Powder are lactose, sodium citrate, and sodium hydroxide.

**Dosage and Administration.** Zovirax® Sterile Powder should be administered only by infusion routes, as a single dose or multiple doses over 1 to 3 hours, as described below.

**INDICATIONS AND USAGE.** Zovirax® Sterile Powder is indicated for the treatment of herpes simplex infections. It is available in a single-dose vial, which contains 1g of sterile powder, and as a multiple-dose vial, which contains 5g of sterile powder.

**CONTRAINDICATIONS.** Zovirax® Sterile Powder is contraindicated in patients who have a history of sensitivity to acyclovir or to any component of Zovirax® Sterile Powder.

**WARNINGS.** Zovirax Sterile Powder is contraindicated in patients who have a history of sensitivity to acyclovir or to any component of Zovirax® Sterile Powder.

**ADVERSE REACTIONS.** The most common adverse reactions associated with Zovirax® Sterile Powder are nausea, vomiting, diarrhea, and abdominal pain. Other possible reactions include fever, headache, and skin rash.

**PRECAUTIONS.** Zovirax® Sterile Powder should be used cautiously in patients with renal impairment or hepatic dysfunction.

**REFERENCES.** For further information, please consult the full prescribing information for Zovirax® Sterile Powder.

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**CLINICAL PHARMACOLOGY.** Zovirax® Sterile Powder is a sterile, white, crystalline powder with a molecular weight of 247,125 daltons. It is available in a single-dose vial containing 1g of sterile powder and as a multiple-dose vial containing 5g of sterile powder.

**HOW SUPPLIED.** Zovirax® Sterile Powder is available in single-dose vials containing 1g of sterile powder and in multiple-dose vials containing 5g of sterile powder.

**PHARMACOKINETICS.** Acyclovir is rapidly absorbed following oral administration. The peak plasma concentration occurs 1 to 2 hours after ingestion. Acyclovir is extensively distributed to body tissues.

**CLINICAL STUDIES.** The efficacy and safety of Zovirax® Sterile Powder have been evaluated in several clinical studies. These studies have demonstrated the effectiveness of Zovirax® Sterile Powder in treating various viral infections.

**REFERENCES.** For further information, please consult the full prescribing information for Zovirax® Sterile Powder.
Hemochromatosis: For patients who require dialysis, the mean plasma half-life of iron is 4 to 6 days, and patients with cirrhosis or diabetes may have a shorter half-life. The mean plasma half-life of iron is determined by the amount of iron removed and the rate of iron absorption from the gut. The mean plasma half-life of iron is determined by the amount of iron removed and the rate of iron absorption from the gut. The mean plasma half-life of iron is determined by the amount of iron removed and the rate of iron absorption from the gut. The mean plasma half-life of iron is determined by the amount of iron removed and the rate of iron absorption from the gut. The mean plasma half-life of iron is determined by the amount of iron removed and the rate of iron absorption from the gut. The mean plasma half-life of iron is determined by the amount of iron removed and the rate of iron absorption from the gut. 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ZOVRAX® (ACYCLOVIR) Ointment 5%

DESCRIPTION: Zoivax is the brand name for acyclovir, an antiviral drug active against herpes viruses. Zoivax Ointment 5% is a formulation for topical administration. Each gram of Zoivax Ointment 5% contains 50 mg of acyclovir in a polyethylene glycol (PEG) base.

The chemical name of acyclovir is 9-(2-hydroxyethyl)methylguanine. It has the following structural formula:

\[
\text{CH}_3\text{O}-\text{CH}_2\text{CH}_2\text{OH}
\]

Acyclovir is a white, crystalline powder with a molecular weight of 225 Daltons, and a maximum solubility in water at 8.4 mg/mL.

CLINICAL PHARMACOLOGY: Acyclovir is a synthetic acyclovir purine nucleoside analogue with in vitro inhibitory activity against herpes simplex types 1 and 2 (HSV-1 and HSV-2), varicella-zoster, Epstein-Barr and cytomegalovirus. In cell cultures, the inhibitory activity of acyclovir for herpes simplex virus is highly selective. Cellular thymidine kinase does not inactivate acyclovir as a substrate. Herpes simplex virus-coded thymidine kinase, however, converts acyclovir into acyclovir monophosphate, a nucleoside monophosphate. The monophosphate is further converted into diphosphate by cellular guanylyl kinase and into triphosphate by a number of cellular enzymes. Acyclovir triphosphate interferes with herpes simplex virus DNA polymerase and inhibits viral DNA replication. Acyclovir monophosphate also inhibits cellular DNA polymerase but to a lesser degree. In vivo, acyclovir triphosphate is incorporated into the growing chains of DNA by viral DNA polymerase and is much more effective in killing cells than the monophosphate.

When incorporation occurs, the DNA chain is terminated. Acyclovir is preferentially taken up and selectively concentrated in the active infected form by herpes virus-infected cells. Thus, acyclovir is much more toxic to virus than to normal uninfected cells. (1) Less is taken up; (2) the drug is converted to the active form; (3) cellular DNA polymerase is less sensitive to the effects of the active form.

The relationship between in vitro susceptibility of herpes simplex viruses to antiviral drugs and clinical response has not been established. The techniques and cell culture types used for determining in vivo susceptibility may influence the results obtained. Using a quantitative assay to determine the acyclovir concentration producing 50% inhibition of virus cytopathic effect (ID50), 28 HSV-1 clinical isolates had a mean ID50 of 0.17 µg/mL and 32 HSV-2 clinical isolates had a mean ID50 of 0.16 µg/mL.

RESULTS from other studies using different assays have yielded mean ID50 values for clinical HSV-1 isolates of 0.019, 0.03, and 0.042 µg/mL and for clinical HSV-2 isolates of 0.027, 0.38, and 0.004 µg/mL, respectively. (2-4)

Two clinical pharmacology studies were performed with Zoivax Ointment 5% in adult immunocompromised patients, at risk of developing mucocutaneous Herpes simplex virus infections or with localized varicella-zoster infections. These studies were designed to evaluate the dermal tolerance, systemic toxicity and percutaneous absorption of acyclovir.

In one of these studies, which included 16 patients, the complete regimen of the vehicle or the vehicle was randomly administered in a dose of 1 cm² strips (5 g acyclovir) four times a day for seven days to an intact skin surface area of 4-7 squares cm. Local irritation, systemic toxicity or cutaneous dermatitis were observed. In addition, no drug was detected in blood and urine by radioimmunoassay, sensitivity, 0.01 µg/mL.

The other study included eleven patients with localized varicella-zoster. The uncontrolled study, acyclovir was detected in the blood of 2 patients and in the urine of all patients tested. Acyclovir levels in plasma ranged from <0.01 to 0.91 ng/mL in eight patients with normal renal function, and from 0.01 to 0.79 ng/mL in one patient with impaired renal function. Acyclovir exceeded the limit ranged from <0.01 to 0.54 ng/mL daily dose. Therefore, systemic absorption of acyclovir after topical application is minimal.

INDICATIONS AND USAGE: Zoivax (Acyclovir) Ointment 5% is indicated in the treatment of initial herpes infections and in limited number of the mucocutaneous Herpes simplex virus infections in immunocompromised patients. Zoivax Ointment 5% has shown a decrease in healing time in a few cases a decrease in duration of viral shedding and duration of pain. In studies in immunocompromised patients with primary herpetic lesions, there was a decrease in duration of viral shedding and a slight decrease in duration of pain. By contrast, in studies of recurrent herpes genitalis and herpes labialis in immunocompromised patients, there was no evidence of clinical benefit; there was some evidence of dermatitis or scaling.

Diagnosis: Whereas cutaneous lesions associated with Herpes simplex infections are often characteristic, the timing of multiloculated giant cell in lesions prepared from lesion exudate or scraping, and the appearance of herpes-specific inclusions in the component cells of the formulation for confirmation of the diagnosis. In genital herpes, appropriate examinations should be performed to rule out other sexually transmitted diseases.

CONTRAINDICATIONS: Zoivax Ointment 5% is contraindicated for patients who develop hypersensitivity to any of the components of the formulation.

WARNINGS: Zoivax Ointment 5% is intended for cutaneous use only and should not be used in the eye.

PRECAUTIONS: General: The recommended dosage, frequency of applications, and length of treatment should be restricted by the determinations of the physician. The use of Zoivax Ointment 5% should be limited to the areas of the body which demonstrate that the use of Zoivax Ointment 5% will either prevent transmission of affection to others or prevent recurrent infections when applied in the absence of signs and symptoms. Zoivax Ointment 5% should not be used for the prevention of recurrent HSV infections. Although clinically significant viral resistance has increased, no resistance has been observed; the possibility exists. Drug Interactions: Clinical experience has identified no interactions resulting from topical or systemic administration of these drugs concurrently with Zoivax Ointment 5%.