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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. 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.

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

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

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)**

- **Vesicles Present**
  - **Darkfield Examination**
    - Positive
      - **Probable Syphilis**
    - Negative
      - **Nontreponemal serological test for syphilis (RPR, VDRL, etc.)**
        - Positive
          - **Probable Syphilis**
        - Negative
          - **History and Exam Suggest Herpes**
            1. History of vesicles
            2. History of recurrences
            3. Exposure to herpes
            4. Painful, superficial lesions
          - **Syphilis**

- **Probable Herpes**
  - **Consider virologic confirmation**
    - **Possible Herpes or Chancre**
      - Obtain virologic confirmation of HSV
        - Positive
          - **Possible Chancre**
            - Obtain culture for *H. ducreyi*
              - Positive
              - **Chancre**
              - **Possible Syphilis**
                - Repeat darkfield examination and serological tests for syphilis
                  - Positive
                  - **Possible Syphilis**
          - Negative
            - **Possible Chancre**
              - Obtain culture for *H. ducreyi*
                - Positive
                - **Chancre**
                - **Possible Syphilis**
                  - Repeat darkfield examination and serological tests for syphilis
                    - Positive
                    - **Possible Syphilis**
          - Negative
            - **Possible Herpes**
              - **Syphilis**

- **No**

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.\textsuperscript{4} 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.\textsuperscript{4} 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.\textsuperscript{5}

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.\textsuperscript{5} 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

![Primary syphilitic chancre at the inoculation site](image1)
![Primary syphilitic chancre on glans penis](image2)
![Primary syphilitic chancre on penile shaft](image3)
![Infectious papular lesions of secondary syphilis on palms](image4)

<table>
<thead>
<tr>
<th>Clues to Differential Diagnosis</th>
<th>Differences</th>
<th>Similarities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Differences</td>
<td>Herpes</td>
<td>Syphilis</td>
</tr>
<tr>
<td>Appearance of primary lesions</td>
<td>Grouped vesicles on a red base; crusts form as lesions dry up, producing erosion, ulcerations, and possible scarring</td>
<td>Usually one sharply demarcated, eroded papule or ulcer</td>
</tr>
<tr>
<td>Induration</td>
<td>None</td>
<td>Firm</td>
</tr>
<tr>
<td>Pain</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>Tender</td>
<td>Nontender</td>
</tr>
</tbody>
</table>
Chancreoid (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 chancreoid in nonwhites, and males appear to have a higher incidence than females. Due to the low incidence of chancreoid 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 chancreoid are present, the diagnostic possibilities are narrowed.6

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

### Clues to Differential Diagnosis3

<table>
<thead>
<tr>
<th>Differences</th>
<th>Similarities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Herpes</strong></td>
<td><strong>Chancreoid</strong></td>
</tr>
<tr>
<td>Appearance of primary lesions</td>
<td>Excavated papule or pustule with yellow-to-gray base and purulent or hemorrhagic secretion; never vesicular</td>
</tr>
<tr>
<td>Grouped vesicles on a red base; crusts form as lesions dry up, producing erosion, ulcerations, and possible scarring</td>
<td>—</td>
</tr>
<tr>
<td>Induration</td>
<td>None</td>
</tr>
<tr>
<td>Pain</td>
<td>More painful in males than females</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>Firm</td>
</tr>
</tbody>
</table>
LYMPHOGRANULOMA VENEREUM (LGV)

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 *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 suppurative — is an important clue to differential diagnosis.9

<table>
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</tr>
<tr>
<td>Herpes</td>
</tr>
<tr>
<td>LGV</td>
</tr>
<tr>
<td>Appearance of primary lesions</td>
</tr>
<tr>
<td>Grouped vesicles on a red base; crusted form as lesions dry up, producing erosions, ulcerations, and possible scarring</td>
</tr>
<tr>
<td>Induration</td>
</tr>
<tr>
<td>Pain</td>
</tr>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Lymph nodes</td>
</tr>
<tr>
<td>Firm</td>
</tr>
</tbody>
</table>
GRANULOMA INGUINALE (GI)

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.\(^\text{11}\)

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.\(^9\)

### Clues to Differential Diagnosis

<table>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Herpes</strong></td>
<td><strong>Granuloma inguinale</strong></td>
</tr>
<tr>
<td>Grouped vesicles on a red base; crusts form as lesions dry up, producing erosions, ulcerations, and possible scarring</td>
<td>Purulent ulcerations, primary lesion begins as indurated nodule, erodes to form beefy, granulomatous raised ulcer</td>
</tr>
<tr>
<td>Lesions may coalesce</td>
<td>Lesions may coalesce</td>
</tr>
<tr>
<td><strong>Induration</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Firm</td>
</tr>
<tr>
<td><strong>Pain</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>Lymph nodes</strong></td>
<td></td>
</tr>
<tr>
<td>Tender, firm</td>
<td>Pseudo-adenopathy</td>
</tr>
</tbody>
</table>

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.

### Clues to Differential Diagnosis

<table>
<thead>
<tr>
<th>Differences</th>
<th>Similarities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Herpes</strong></td>
<td><strong>Molluscum contagiosum</strong></td>
</tr>
<tr>
<td>Appearance of primary lesions</td>
<td>Small, firm umbilicated papules may be flesh-colored, white, translucent, or, rarely yellow</td>
</tr>
<tr>
<td>Induration</td>
<td>None</td>
</tr>
<tr>
<td>Pain</td>
<td>Common</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>Tender, firm</td>
</tr>
</tbody>
</table>

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.
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.

**Clues to Differential Diagnosis**

<table>
<thead>
<tr>
<th>Herpes</th>
<th>Scabies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Appearance of primary lesions</strong></td>
<td><strong>Linear burrows in interdigital spaces and on penis. Red, edematous, often excoriated papules. Long-standing disease may produce larger, firm, red papules (sebatic nodules) especially on the elbows and penis.</strong></td>
</tr>
<tr>
<td>Grouped vesicles on a red base; crusts form as lesions dry up, producing erosions, ulcerations, and possible scarring</td>
<td></td>
</tr>
<tr>
<td><strong>Urticaria/Pain</strong></td>
<td>Pain is common with genital herpes</td>
</tr>
<tr>
<td><strong>Mode of Transmission</strong></td>
<td>Most frequently, through close contact with a person who is shedding virus</td>
</tr>
</tbody>
</table>

Scabies frequently coexists with other STDs including genital warts.

Scabies infections can be transmitted nonsexually between close family members, eg, this prepubertal boy.

Burrows and papules in the interdigital area and on the penis are highly suggestive of scabies.
Genital warts are known by many different names: fillet 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.

<table>
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<tr>
<td>Differences</td>
</tr>
<tr>
<td>Herpes</td>
</tr>
<tr>
<td>Appearance of primary lesions</td>
</tr>
<tr>
<td>Never vesicular unless burned, frozen, or severely traumatized. Typically flesh-colored to slightly pigmented or red. Firm or filiform, friable, and often bleed easily.</td>
</tr>
</tbody>
</table>

Penile warts are frequently seen in patients with other STDs, including genital herpes.

Central ulcerations of early squamous cell carcinoma that developed from wart should not be confused with discrete ulcerations of genital herpes.

Wide and flat vaginal warts with erosions, bleeding, and crust formation may mimic genital herpes.
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.

**Seborrheic dermatitis**
A very common papulosquamous skin disease; look for other commonly affected areas such as nasolabial folds on the face and midanterior chest.
**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.

**Trauma, continued**
Superficial ulceration of penile shaft secondary to trauma.

**Ecchymosis and hyper-pigmentation secondary to trauma**

**Purpura secondary to intercourse**

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

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

**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.

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

**Classic target lesions on the hand**

**Balanitis circinata 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.
Balanitis circumspecta

Atrophy 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.

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.

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.

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.
Both margined and nonmargined 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 anti-viral 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 ten days. This treatment shortens the median duration of the first episodes, reduces healing time, and rapidly stops viral shedding. 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 (200 mg by mouth) three to five times daily reduces the frequency of active disease by 75% - 80% among patients with frequent (at least six/year) recurrences. The dose of ZOVIRAX must be individualized. Patients with less frequent recurrences may take a five-day course of therapy: from onset of prodrome, ZOVIRAX Capsules, 200 mg five times a day for five 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 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; use of condoms and/or spermicidal jelly or cream can help minimize risk.

Due to the increased risk of cervical cancer, women with genital herpes should have annual Papanicolaou smears. 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®
(acyclovir)
CAPSULES

DESCRIPTION: Zovirax is the brand name for acyclovir, an antiviral drug. Zovirax Capsules are a formulation for oral administration. Each capsule of Zovirax contains 200 mg of acyclovir and the inactive ingredients corn starch, lactose, magnesium stearate, and sodium lauryl sulfate. The gelatin capsule contains FD&C Blue No. 2 and other ingredients. Printed with edible black ink.

The chemical name of acyclovir is 9-(2-hydroxyethoxy)methylguanine; it has the following structural formula:

```
\[\text{CH}_3\text{O}\text{C}_2\text{H}_4\text{O}\text{CH}_2\text{CH}_2\text{CH}_3\]
```

Acyclovir is a white, crystalline powder with a molecular weight of 235.25, and a maximum solubility in water is 0.02 mg/mL at 37°C.

CLINICAL PHARMACOLOGY: Acyclovir is a synthetic acyclic purine nucleoside analogue and is cytotoxic to herpes simplex virus type 1 and 2 (HSV-1, HSV-2), varicella-zoster virus (VZV), cytomegalovirus (CMV). In cells infected with HSV, the herpes simplex virus DNA polymerase incorporates acyclovir triphosphate into viral DNA. Acyclovir triphosphate is phosphorylated by cellular kinases to acyclovir monophosphate, which is phosphorylated sequentially by cell VIA and cell VIA to form acyclovir triphosphate. The triphosphate enters the viral capsid and inhibits viral DNA polymerase activity. In cells infected with CMV, the herpes simplex virus DNA polymerase incorporates acyclovir triphosphate into viral DNA. Acyclovir triphosphate is phosphorylated by cellular kinases to acyclovir monophosphate, which is phosphorylated sequentially by cell VIA and cell VIA to form acyclovir triphosphate. The triphosphate enters the viral capsid and inhibits viral DNA polymerase activity.

The therapeutic effectiveness of Zovirax in treating herpes simplex virus infections has been demonstrated in a variety of clinical settings. In patients with herpes labialis, the oral administration of Zovirax significantly reduced the duration of symptoms and the severity of lesion. In patients with herpes zoster, Zovirax significantly reduced the duration of symptoms and the severity of lesion. In patients with recurrent genital herpes, Zovirax significantly reduced the duration of symptoms and the severity of lesion.

Recurrent Episodes: Double-blind, placebo-controlled studies have shown that Zovirax Capsules are effective in the treatment of recurrent genital herpes. The results of these studies indicate that Zovirax Capsules are effective in reducing the duration of symptoms and the severity of lesion in patients with recurrent genital herpes.

Diagnosis: The presence of viral lesions associated with herpes simplex virus infections is often characteristic in appearance. However, other etiologic agents may cause similar lesions. Clinical and laboratory tests are utilized to establish presumptive evidence of herpesvirus infection. Smears prepared from lesions or scrapings may be stained with Wright or Giemsa stains and examined for the presence of multinucleated giant cells (TRICHOMA). Preparation of HSV from herpes simplex virus infection. Smears may also be treated in other test systems for herpes.

CONTRAINDICATIONS: Zovirax Capsules are contraindicated for patients who develop hyperosmolar or intolerance to the components of the formulation.

WARNINGS: Zovirax Capsules are contraindicated for oral ingestion only.

PRECAUTIONS: General: Zovirax has caused decreased sperm motility at high doses in some animals and mutagenesis in some acute studies at high concentrations of drug (see PRECAUTIONS — Carcinogenesis, Mutagenesis, Impairment of Fertility). The recommended dosage and length of treatment should not be exceeded (see DOSAGE AND ADMINISTRATION).

Exposure of Herpes simplex isolates to acyclovir in vitro can lead to the emergence of resistant isolates. The possibility of the appearance of less sensitive isolates may be important when treating patients. The relationship between the in vitro sensitivity of Herpes simplex virus to acyclovir and clinical response to therapy has yet to be established (see CLINICAL PHARMACOLOGY). Because of the possibility that less sensitive variants may be selected in patients who are receiving acyclovir, all patients should be advised to take particular care to avoid potential transmission of virus to others while they are on therapy. In severely immunocompromised patients, the physician should be aware that prolonged or repeated courses of acyclovir may result in selection of resistant viruses which may not fully respond to continued acyclovir therapy.

Information for Patients: Educational material is being provided to pharmacists and other health care professionals to give to patients. It is important, in part, the following information:

Genital herpes is a sexually transmitted disease and patients should avoid intercourse when visible lesions are present because of the risk of infecting intimate partners. Zovirax (acyclovir) Capsules are for oral ingestion only. Medication should not be shared with others. The prescribed dosage should not be exceeded. Patients with severe immunodeficiency may not be able to eliminate latent viruses. Some patients experience increased severity of the first episode following cessation of therapy; the severity of subsequent episodes and the effect on the natural history of the disease are still under study.

There are still unanswered questions concerning protracted genital and
mutations; long-term studies are continuing. Decreased sperm production has been seen at high doses in some animal preliminary analysis of a study using 400 mg or 1000 mg/kg per day for 28 days in rats. Chronic treatment with Zovirax did not cause any significant changes in sperm production. Patients who have had exposure to Zovirax during pregnancy should be encouraged to use alternative methods of contraception.

Drug Interactions: Co-administration of probenecid with intravenous acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of 50, 150, and 450 mg/kg given by gavage. There was no evidence of any significant increase in the incidence of tumors in rats treated with acyclovir. Acyclovir-induced tumors were not found in a 2-year bioassay in male and female rats at doses of 250 and 500 mg/kg/day, respectively.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Acyclovir was not teratogenic in the mouse (400 mg/kg/day, p.o.) or rat (50 mg/kg/day, s.c. or i.v.). In a 4-week teratogenicity study in the rat, no evidence of developmental toxicity was observed at doses up to 400 mg/kg/day.

Pitfalls to Consider: Before starting treatment with Zovirax, patients should be encouraged to use alternative methods of contraception. Patients who have had exposure to Zovirax during pregnancy should be encouraged to use alternative methods of contraception.

Drug Interactions: Co-administration of probenecid with intravenous acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced.
ZOVIRAX®
(acyclovir sodium)
STERILE POWDER
FOR INTRAVENOUS INFUSION ONLY

DESCRIPTION: Zovirax is the brand name for acyclovir, an antiviral drug active against herpesviruses. Zovirax Sterile Powder is a formulation for intravenous administration. Each vial of Zovirax Sterile Powder contains 500 mg of sterile lyophilized acyclovir sodium equivalent to 500 mg of acyclovir.

The chemical name of acyclovir sodium is 9-[(2-hydroxyethoxy)methyl]guanidine; it has the following structural formula:

![Structural formula of acyclovir sodium](image)

Acyclovir sodium is a white, crystalline powder with a molecular weight of 247 daltons, and a solubility in water exceeding 100 mg/mL. Recommended reconstitution with 10 mL of 1% dextrose in water yields 50 mg/mL acyclovir (at pH approximately 11). Further dilution in any appropriate intravenous solution must be performed before infusion (see Method of Preparation). At physiological pH, acyclovir exists as the un-ionized form with a molecular weight of 225 daltons and a maximum solubility of 2.5 mg/mL at 37°C.

CLINICAL PHARMACOLOGY: Acyclovir is a synthetic acyclic purine nucleoside analogue with in vitro and in vivo inhibitory activity against Herpes simplex, 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 effectively utilize acyclovir as a substrate. Herpes simplex virus-coded thymidine kinase, however, converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes. Acyclovir triphosphate interferes with the synthesis of viral DNA by incorporating into the viral DNA polymerase to a lesser degree. In vitro, acyclovir triphosphate can be incorporated into growing chains of DNA by viral DNA polymerase to a much smaller extent by cellular DNA polymerase. When incorporation occurs, the DNA chain is terminated. Acyclovir is preferentially incorporated into the active triphosphate form by herpesvirus-infected cells. Thus, acyclovir is much less toxic in vitro for normal uninfected cells because: (1) less is taken up; (2) less 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 virus to antiviral drugs and clinical response has not been established. The techniques and cell types used for determining in vitro susceptibility may influence the results obtained. With a quantitative assay to determine the acyclovir concentration producing 50% inhibition of viral cytopathic effect (100% of virus-infected cells had a mean ID₅₀ of 0.73 µg/mL and 32 HSV-2 clinical isolates had a mean ID₅₀ of 0.99 µg/mL). Results from other studies using different assays have yielded mean ID₅₀ values for clinical HSV-1 isolates of 0.018, 0.03 and 0.04 µg/mL and for clinical HSV-2 isolates of 0.02, 0.03 and 0.03 µg/mL, respectively. Pharmacokinetics: The pharmacokinetics of acyclovir has been evaluated in 85 patients (8 studies). Results were obtained in adult patients with normal renal function during Phase III trials after single doses ranging from 0.5 to 15 mg/kg and after multiple doses ranging from 2.5 to 10 mg/kg every 8 hours. Pharmacokinetics was also determined in pediatric patients with normal renal function ranging in age from 1 to 17 years at doses of 250 mg/kg to 500 mg/kg every 8 hours. In these studies, dose-independent pharmacokinetics is observed in the range of 0.5 to 15 mg/kg. Proportionality between dose and plasma levels is seen after single doses or at steady state after multiple dosing. When Zovirax was administered to children at 5 mg/kg (approximately 250 mg/kg) by 1-hr infusions every 8 hours, mean steady-state peak and trough concentrations of 1.5 to 2.5 mg/mL, respecively, were achieved. Similar concentrations are achieved in children over 1 year of age when doses of 250 mg/kg are given every 8 hours. Concentrations achieved in the cerebrospinal fluid are approximately 50% of plasma values. Plasma protein binding in in vitro studies is relatively low (9% to 20%) and drug interactions involving binding site displacement are not anticipated.

Refral rectal infusion of drug by hypodermal injection and tubular secretion is the major route of acyclovir elimination in adults with renal function relatively normal. A significant amount of drug is reformed in feces and expired, so there is evidence for a large hepatic deactivation of acyclovir. However, postmortem examinations have shown that acyclovir is widely distributed in tissues and body fluids including brain, kidney, lung, liver, muscle, spleen, uterus, vaginal mucosa, vaginal secretions, cecum, pancreas fluid and hepatic vein fluid.

In a phase I study in 3 adult volunteers, 1 g of probenecid was administered orally prior to a single 5-mg/kg intravenous infusion of acyclovir. The acyclovir half-life and area under the plasma concentration-time curve increased by 15% and 40%, respectively, compared to a control infusion of acyclovir without probenecid. The mean urinary excretion of acyclovir decreased from 70% to 69% of the dose indicating that probenecid can influence the renal excretion of acyclovir.

The half-life and total body clearance of acyclovir is dependent on renal function as shown below:

<table>
<thead>
<tr>
<th>Creatinine Clearance (ml/min)</th>
<th>Half-Life (hr)</th>
<th>Total Body Clearance (ml/min/1.73m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 80</td>
<td>2.5</td>
<td>227</td>
</tr>
<tr>
<td>50-80</td>
<td>3.4</td>
<td>216</td>
</tr>
<tr>
<td>30-50</td>
<td>5.5</td>
<td>184</td>
</tr>
<tr>
<td>0 (Anuric)</td>
<td>10.5</td>
<td>100</td>
</tr>
</tbody>
</table>

Zovirax was administered at a dose of 2.5 mg/kg to 6 adult patients with severe renal failure. The peak and trough plasma levels during the 47 hours preceding hemodialysis were 8.6 µg/mL and 0.7 µg/mL, respectively.

CONSULT DOSAGE AND ADMINISTRATION section for recommended adjustments in dosing based on creatinine clearance.

The half-life and total body clearance of acyclovir in pediatric patients over 1 year of age is similar to those in adults with normal renal function (see DOSAGE AND ADMINISTRATION).

INDICATIONS AND USAGE: Zovirax Sterile Powder is indicated for the treatment of initial and recurrent mucosal and cutaneous Herpes simplex virus (HSV-1 and HSV-2) infections in immunocompromised adults and children. It is also indicated for severe initial clinical episodes of genital herpes in patients who are not immunocompromised.

These indications are based on the results of several double-blind, placebo-controlled studies which evaluated the drug's effect on virus excretion, complete healing of lesions, and relief of pain.

Herpes Simplex Infections in Immunocompromised Patients

A multicenter trial of Zovirax Sterile Powder at a dose of 250 mg/M² every 8 hours (750 mg/M²/day) for 7 days was conducted in 97 immunocompromised patients with orofacial, esophageal, genital and other localized infections (60 treated with Zovirax and 47 with placebo). Zovirax significantly decreased virus excretion, reduced pain, and promoted healing and rapid resolution of lesions.

Initial Episodes of Herpes Genitalis

A controlled trial was conducted in 25 patients with severe initial episodes of herpes genitalis treated with a Zovirax dosage of 5 mg/kg every 8 hours for 5 days (22 patients treated with Zovirax and 15 with placebo). Significant treatment effects were seen in elimination of virus from lesions and in reduction of healing times.

In a similar study, 15 patients with initial episodes of genital herpes were treated with Zovirax 5 mg/kg every 8 hours for 5 days and 15 with placebo. Zovirax decreased the duration of viral excretion, new lesion formation, duration of vesicles and promoted more rapid healing of all lesions.

Diagnosis

The use of appropriate laboratory diagnostic procedures will help to establish the etiologic diagnosis. Positive cultures for Herpes simplex virus offer a reliable means for confirmation of the diagnosis. In initial episodes of genital herpes, appropriate examinations should be performed to rule out other sexually transmitted diseases. Whereas cutaneous lesions caused by Herpes simplex infections are often characteristic, the finding of multinucleated giant cells in smears prepared from lesion exudate or scrapings may assist in the diagnosis.

CONTRAINDICATIONS: Zovirax (acyclovir sodium) Sterile Powder is contraindicated for patients who have developed hypersensitivity to the drug.

WARNINGS: Zovirax Sterile Powder is intended for intravenous infusion only, and should not be administered topically, intramuscularly, orally, subcutaneously, or in the eye.

Intravenous infusions must be given over a period of at least 1 (one) hour to prevent renal tubular damage (see PRECAUTIONS AND DOSAGE AND ADMINISTRATION).

PRECAUTIONS: General: The recommended dosage, frequency, and length of treatment should not be exceeded (see DOSAGE AND ADMINISTRATION).

Although the aqueous solubility of acyclovir sodium (for infusion) is >100 mg/mL, precipitation of acyclovir crystals in renal tubules can occur if the maximum solubility of free acyclovir (2.5 µg/mL at 37° C in water) is exceeded if the drug is administered by bolus injection. This complication causes a rise in serum creatinine and blood urea nitrogen (BUN), and a decrease in renal creatinine clearance. Ensuring renal tubular damage can prevent acute renal failure.

Abnormal renal function (decreased creatinine clearance) can occur as a result of acyclovir administration and depends on the state of the patient's hydration, other treatments, and the rate of drug administration. Reliable administration of the drug leads to a 10% incidence of renal dysfunction, while in controlled studies, infusion of 5 mg/kg every 8 hours over an hour was associated with a lower frequency — 4.6%. Concurrent use of other nephrotoxic drugs, pre-existing renal disease, and dehydration make further renal impairment with acyclovir more likely. In most instances, alterations of renal function were transient and resolved spontaneously or with improvement of water and electrolyte balance, drug dosage adjustment or discontinuation of drug administration. However, in some instances, these changes may progress to acute renal failure.

As administration of Zovirax by intravenous infusion must be accompanied by adequate hydration. Since maximum urine concentration occurs within the first 2 hours following infusion, particular attention should be given to establishing sufficient urine flow during that period in order to prevent precipitation in the renal tubules.

When dosage adjustments are required they should be based on estimated creatinine clearance (see DOSAGE AND ADMINISTRATION).

Although rarely, 1% of patients receiving intravenous acyclovir have manifested encephalopathic changes characterized by lethargy, obtundation, tremors, confusion, hallucinations, agitation, seizures or coma. Zovirax should be used with caution in these patients who have underlying neurologic abnormalities and those with serious renal, hepatic, or electrolyte abnormalities or significant hypoxia. It should also be used with caution in patients who have manifested prior neurologic reactions to cytotoxic drugs or
those receiving coadministered intravenous methotrexate or interferon.

Exposure of HSV isolates to acyclovir in vitro can lead to the emergence of less sensitive viruses. These viruses usually are deficient in thymidine kinase (required for acyclovir activation) and are less pathogenic in animals. Similar isolates have been observed in severely immunocompromised patients during the course of controlled and uncontrolled studies of intravenously administered Zovirax. These occurred in patients with congenital severe combined immunodeficiencies or following bone marrow transplantation. The presence of these viruses was not associated with a worsening of clinical illness and, in some instances, the virus disappeared spontaneously. The possibility of the appearance of less sensitive viruses must be borne in mind when treating such patients. The relationship between the in vitro sensitivity of herpesviruses to acyclovir and clinical response to therapy has yet to be established.

Drug Interactions: Co-administration of probenecid with acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced. Clinical experience has identified no other significant interactions resulting from administration of other drugs concomitantly with Zovirax (acyclovir sodium) Sterile Powder.

Carcinogenesis: Mutagenic and Carcinogenicity Studies: Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of 50, 150 and 450 mg/kg given by gavage. There was no statistically significant difference in the incidence of tumors between treated and control animals, neither was any increase in the latency of tumors. In 21 in vitro cell transformation assays, used to provide preliminary assessment of potential carcinogenicity in advance of these more definitive lifetime bioassays in rodents, considerable variation in results was obtained. Acyclovir was positive at the highest dose used in one system and the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice. Acyclovir was negative in another cell transformation system.

No chromosome damage was observed at maximum tolerated parenteral doses of 100 mg/kg acyclovir in rats or Chinese hamsters; higher doses of 500 and 1000 mg/kg were clastogenic in Chinese hamsters. In addition, no activity was found in a dominant lethal study in mice. In 9 of 11 microbial and mammalian cell assays, no evidence of mutagenicity was observed. In 2 mammalian cell assays (human lymphocytes and L5178Y mouse lymphoma cells) as short-term, positive responses were noted, but chromosome damage occurred, but only at concentrations at least 25 times the acyclovir plasma levels achieved in man.

Acyclovir does not impair fertility or reproduction in mice at oral doses up to 450 mg/kg. In female rabbits treated subcutaneously with acyclovir subsequent to mating, there was a statistically significant decrease in implantation efficiency but no concomitant decrease in litter size at a dose of 50 mg/kg/day.

Pregnancy: Teratogenic Effects. Pregnancy Category C. Acyclovir was not teratogenic in the mouse (500 mg/kg/day, p.o.), rabbit (50 mg/kg/day, s.c.) or rat (50 mg/kg/day, s.c.). Although maximum tolerated doses were tested in the teratology studies, the plasma levels obtained did not exaggerate maximal plasma levels that might occur in clinical use of intravenous acyclovir.

There have been no adequately and well-controlled studies in pregnant women. Acyclovir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Zovirax is administered to a nursing woman.

ADVERSE REACTIONS: The most frequent adverse reactions reported during controlled clinical trials in 164 patients were the following: at the injection site following intravenous administration of the I.V. fluid in 9 (1.4%), transient elevations of serum creatinine in 8 (4.7%), and rash or hives in 3 (1.8%). Less frequent adverse reactions were diaphoresis, hematuria, hypotension, headache and nausea, each of which occurred in 1 patient (1%).

Of the 62 patients receiving placebo, 3 (4.8%) experienced influenza-like illness, 1 (1.6%) experienced respiratory infection, 1 (1.6%) had no change, 1 (1.6%) had no change with changes consistent with bacterial anemia on peritoneal biopsy; another immunocompromised patient exhibited crossed tendon and bunion.

Additional adverse reactions were reported during uncontrolled trials. The most frequent adverse reactions were reported in 6 (1.5%) of the patients; occurrence was in 16% of patients, usually following rapid (less than 10 minutes) intravenous infusion. Less frequent adverse reactions were thrombocytopenia and jitters, each in 0.4% of patients. A total of 18% of patients have had headaches.

OVERDOSE: Overdosage has been reported following administration of bolus injections, or inappropriately high doses, and in patients whose fluid and electrolyte balance was not properly maintained. This has resulted in elevations in BUN, serum creatinine and subsequent renal failure.

Precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) in the intratubular fluid is exceeded (see PRECAUTIONS). A 10% reduction occurs in plasma acyclovir concentrations. Data concerning peritoneal dialysis are incomplete but indicate that this method may be significantly less efficient in removing acyclovir from the blood. The time of acute renal failure and amnion, the patient may benefit from drug removal until renal function is restored (see DOSAGE AND ADMINISTRATION).

DOSAGE AND ADMINISTRATION: CAUTION — RAPID OR BOLUS INTRAVENOUS INJECTION IS PROHIBITED. INJECT INTO INTRAMUSCULAR OR SUBCUTANEOUS INJECTION MUST BE AVOIDED.

Dosage: MUCOSAL AND CUTANEOUS HERPES SIMPLEX (HSV-1 and HSV-2)
DESCRIPTION: Zovirax is the brand name for acyclovir, an antiviral drug active against herpes viruses. Zovirax Ointment 5% is a formulation for topical administration. Each gram of Zovirax Ointment 5% contains 50 mg of acyclovir in a polyethylene glycol (PEG) base.

The chemical name of acyclovir is 9-(2-hydroxyethoxy)methyl guanine; it has the following structural formula:

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

Acyclovir is a white, crystalline powder with a molecular weight of 255.26 Daltons, and a maximum solubility in water of 1.3 mg/mL.

CLINICAL PHARMACOLOGY: Acyclovir is a synthetic acyclic purine nucleoside analogue with in vitro inhibitory activity against Herpes simplex type 1 and 2 (HSV-1 and HSV-2), varicella-zoster, Epstein-Barr and cytomegalovirus. In cell cultures, the 50% inhibitory concentration of acyclovir against Herpes simplex virus is highly selective. Cellular thymidine kinase does not effectively utilize acyclovir as a substrate. Herpes simplex virus-coded thymidine kinase, however, converts acyclovir into acyclovir monophosphate, a nucleotide. The monophosphate is further converted into diphosphate by cellular guanylate 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 triphosphate also inhibits cellular α-β-DNA polymerase but to a lesser degree. In vitro, acyclovir triphosphate can be incorporated into growing chains of DNA by viral DNA polymerase and to a much smaller extent by cellular α-β-DNA polymerase. When incorporation occurs, the DNA chain is terminated. Acyclovir is preferentially taken up and selectively converted to the active triphosphate form by herpesvirus-infected cells. Thus, acyclovir is much less toxic in vitro for normal uninfected cells because: 1) less is taken up; 2) less is converted to the active form; 3) cellular α-β-DNA polymerase is less sensitive to the effects of the active form.

The relationship between in vitro susceptibility of Herpes simplex virus to antiviral drugs and clinical response has not been established. The techniques used for determining in vitro susceptibility may influence the results obtained. Using a quantitative assay to determine the acyclovir concentration producing 50% inhibition of viral cytopathic effect (ID_{50}) in HSV-1 clinical isolates had a mean ID_{50} of 0.17 μg/mL and 32 HSV-2 clinical isolates had a mean ID_{50} of 0.40 μg/mL. Results from other studies using different assays have yielded mean ID_{50} values for clinical HSV-1 isolates of 0.018, 0.03 and 0.06 μg/mL and for clinical HSV-2 isolates of 0.077, 0.08 and 0.08 μg/mL, respectively.

Two clinical pharmacology studies were performed with Zovirax 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 topical antiviral action and systemic absorption of acyclovir. In one of these studies, which included 16 patients, the complete ointment or its vehicle were randomly administered in a dose of 1 cm strips (26 mg acyclovir) four times a day for seven days to herpes genitalis lesions with localized varicella-zoster. There was no significant systemic toxicity or contact dermatitis observed. In addition, no drug was detected in blood and urine by radioimmunoassay (sensitivity, 0.01 μg/mL).

The other study included 11 patients with 31 lesions of genital herpes and varicella-zoster. In this uncontrolled study, acyclovir was detected in the blood of 9 patients and in the urine of all patients tested. Acyclovir levels in plasma ranged from <0.01 to 0.25 μg/mL in eight patients with normal renal function, and from <0.01 to 0.78 μg/mL in one patient with impaired renal function. Acyclovir excreted in the urine ranged from 0.02 to 9.4 percent of the daily dose. Therefore, systemic absorption of acyclovir after topical application is minimal.

INDICATIONS AND USES: Zovirax (Acyclovir) Ointment 5% is indicated in the management of initial herpes genitalis and in limited non-life-threatening mucocutaneous Herpes simplex virus infections in immunocompromised patients. In clinical trials of initial herpes genitalis, Zovirax Ointment 5% has shown a decrease in healing time and in some cases a decrease in duration of viral shedding and duration of pain. In studies in immunocompromised patients, 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 of herpes labialis in immunocompromised patients, there was no evidence of clinical benefit; there was some decrease in duration of viral shedding.

Diagnosis: Whereas cutaneous lesions associated with Herpes simplex infections are often characterized, the findings of inactivated giant cells in smears prepared from lesions cutaneous or in scrapings may assist in the diagnosis. Positive cultures for Herpes simplex virus offer a reliable means for confirmation of the diagnosis. In genital herpes, appropriate examinations should be performed to rule out other sexually transmitted diseases.

CONTRAINDICATIONS: Zovirax Ointment 5% is contraindicated for patients who develop hypersensitivity or chemical intolerance to the components of the formulation.

WARNING: Zovirax 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 not be exceeded. USE IN CHILDREN AND ADULTS: There is no data to demonstrate that the use of Zovirax Ointment 5% will either prevent transmission of infection to other persons or prevent recurrent infections when applied in the absence of signs and symptoms. Zovirax Ointment 5% should not be used for the prevention of recurrent HSV infections. Although clinically significant viral resistance associated with the use of Zovirax (Acyclovir) Ointment 5% has not been observed, this possibility exists.

Drug Interactions: Clinical experience has identified no interactions resulting from topical or systemic administration of drugs concurrently with Zovirax Ointment 5%.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of 50, 150 and 450 mg/kg/day given by gavage. These studies showed no statistically significant difference in the incidence of malignant and non-malignant tumors in drug-treated animals as compared to controls. In 2 in vivo cell transformation assays, used to provide preliminary assessment of potential mutagenic activity in vivo, both the increased incidence of tumors observed in drug-treated animals as compared to controls. Acyclovir was positive at the highest dose used in one system and the resulting morphologically transformed cells formed tumors when transplanted into immunosuppressed, syngeneic, nude mice. Acyclovir was negative in another transformation system.

No chromosome damage was observed at maximum tolerated parenteral doses of 100 mg/kg for 1 week in mice or rats or in 100 mg/kg for up to 6 months in rabbits. In rabbits given a high dose of acyclovir (60 mg/kg/day, s.c.), there was a statistically significant decrease in implantation efficiency.

Fertility: Teratogenic Effects: Pregnancy Category C. Acyclovir has been known to cause a statistically significant increase in absolute implantation rate when administered to pregnant rabbits, but this was not shown in the mouse. This increased implantation rate was not shown at doses of 20 mg/kg/day in rabbits or 4 mg/kg/day in mice. Therefore, the increased implantation rate should be considered a false positive result.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Zovirax is administered to a nursing woman.

ADVERSE REACTIONS: Because ulcerated genital lesions are characteristic tender and sensitive to any contact or manipulation, patients may experience discomfort upon application of ointment. In the controlled clinical trials, mild pain (including transient sensations of burning and stinging) was reported by 10% (26.9%) of 364 patients treated with acyclovir and by 11% (31.1%) of 170 patients treated with placebo; treatment was discontinued in 2 of these patients. Other local reactions among acyclovir-treated patients included pruritis in 1.4% and rash in 0.3%. Among the placebo-treated patients, pruritis was reported by 17% (6.6%) and rash by 1% (0.3%). In all studies, there were no significant differences between the drug and placebo group in the number of type of reported adverse reactions nor were there any differences in abnormal clinical laboratory findings.

OVERDOSAGE: Overdose by topical application of Zovirax Ointment 5% is unlikely because of limited transdermal absorption (see Clinical Pharmacology). DOSE AND ADMINISTRATION: Apply sufficient quantity to adequately cover all lesions every 3 hours 6 times per day for 7 days. The dose size per application will vary depending upon the lesion area but should approximate a one-inch ribbon of ointment per 4 square inches of surface area. A flared cup or rubber glove should be used when applying Zovirax to prevent contamination of other body sites and transmission of infection to other persons. Therapy should be initiated as early as possible following onset of signs and symptoms.

HOW SUPPLIED: Zovirax Ointment 5% is supplied in 15 g tubes (NDC 0001-0903-94). Each gram contains 50 mg acyclovir in a polyethylene glycol base. Store at 15°-25°C (59°-77°F) in a dry place.

ANIMAL PHARMACOLOGY AND ANIMAL TOXICITY: Topical treatment of guinea pigs with 10% acyclovir in polyethylene glycol ointment for three weeks did not result in cutaneous irritation or systemic toxicity. Also, a wide variety of animal tests by standard routes demonstrated that acyclovir has a low order of toxicity.

Acyclovir did not cause dermal sensitization in guinea pigs.

REFERENCES:

U.S. Patent No. 4196674