AESGP
VOICE OF EUROPEAN SELF-CARE INDUSTRY

AESGP Evidence Paper

Antivirals used in the self-care sector

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Introduction

AESGP supports the revision of the EU pharmaceutical law and the Commission's intention to modernize the EU pharmaceuticals regulatory environment. AESGP is, however, concerned that some **provisions could result in unintended consequences such as the restriction of access to commonly used non-prescription medicines. For example, the proposal to restrict access to common antifungal and antiviral non-prescription medicines by making them subject to prescription.**

While supporting the European Action Plan against Antimicrobial Resistance and the objectives of the Chemical Strategy for Sustainability, AESGP believes that the **prescription status of antimicrobial products (in particular, antifungals and antivirals) should be restricted to those products for which an AMR risk has been confirmed as a public health threat.**

This proposal would make all antifungal and antiviral medications that are currently available over the counter to treat minor conditions like athletes' foot, lip herpes (cold sores), skin warts, dandruff, vaginal thrush, minor eye infections in otherwise healthy citizens only available via prescription from a doctor.

Making treatments for these infections prescription-only will negatively impact European citizens and have significant impact on healthcare systems. Instead of getting advice and access to treatments in their local pharmacy, citizens would have to visit a Family Doctor or a General Practitioner for a prescription. This would increase health care costs and add pressure to already-stretched health systems and would ultimately impact how quickly such simple conditions can be treated. Delaying treatment could increase severity and transmission of these infections further exacerbating the situation.

We consider that this proposal is a disproportionate and unnecessary risk mitigation since there is no evidence to suggest that self-care usage of antifungal or antiviral medicinal products give rise to antimicrobial resistance.

- The risks of resistance are linked with specific underlying conditions (e.g., immunocompromised patients) for which antivirals and antifungals are prescribed at high doses and via systemic routes. The risk of resistance in these populations is accrued if the antifungal/antivirals are used inappropriately, especially during long course of systemic treatments.

- Non-prescription antiviral and antifungals have well defined indicated usages and are generally used in lower doses and via topical routes of administration. There is no evidence that non-prescription medicines are associated with AMR.

- The proposal to restrict all antifungals and antimicrobials to prescription legal status would not answer the current problem of AMR. Instead, it would deprive people suffering from self-limiting conditions from fast access to efficacious treatments. It would drive an unnecessary need of doctors' resources whilst adding cost to already stretched national health funds. Furthermore, a fast onset of treatment is mandatory for those minor conditions not to spread or aggravate (e.g., *tinea inguinalis* can spread to the genital area) resulting in worsened clinical outcomes.

- A case-by-case decision on prescription status taken by regulatory authorities on each medicinal product at time of marketing authorization approval is a more appropriate and proportionate approach.

Summary

The WHO highlights antiviral drug resistance as problems in the immunocompromised people, especially in the treatment of HIV, where these drugs are already prescription controlled (1). According to the WHO, the underlying problems of HIV drug resistance lie more in the limited access to medication and lack of treatment adherence (2). These are the underlying problems for viral treatments, rather than drug resistance and prescribing-status.

As mentioned above the heterogenous group of immunocompromised people, which makes up about 2–3% of the overall population, includes people with human immunodeficiency virus (HIV) infection, cancers, transplants, primary immunodeficiencies and those treated with immunosuppressive biologics and medications. Their underlying aetiologies and demographics contribute to multifactorial and interrelated causes for immune compromise. In addition to impaired responses to infection, immunocompromised patients tend to be older, have additional comorbid conditions beyond immunosuppression, and have fewer reserves to recover from the physiological challenges of acute infection (Shoham et al 2023). Taken this into account, these patients are under medical treatment anyway, because of their underlying health condition and will therefore, always consult their medical attending physician before taking any medication. Thus, OTC or Rx status of the medicine is not relevant for this patient population, because any medication will be taken in consultation with the corresponding physician.

Acyclovir (ACV) and penciclovir are pharmacologically inactive substances that become a virostatic only after penetration into a cell infected with HSV type 1 and type 2, varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr Virus (EBV), and human herpes virus 6 (HHV-6). Due to the need to be phosphorylated by a viral thymidine kinase, only present in virus-infected cells, the effect is highly virus selective (3).

Recurrent herpes labialis is a common painful condition, due to the activation of an infection with the herpes simplex virus (HSV-1) (the causative agent of cold sores). The herpes viruses settle in the nodes (ganglia) of the facial nerve (trigeminal nerve). If the disease breaks out, they migrate along the nerve fibres into the lips and trigger the typical symptoms. Anyone who has been infected with herpes viruses once carries them for life. Herpes on the lips mainly breaks out when the immune system is weakened or challenged - for example, during a cold or after strenuous physical exertion. Stress, hormonal fluctuations and skin irritation, for example due to sunlight, are also considered possible triggers (4).

A study by the World Health Organization (WHO) in 2020 showed a global prevalence of HSV-1 in 66.6% of the world population aged 0-49 years in 2016 (James C et al. 2020). The probability of infection increases with age.

Characteristic signs and symptoms allow early detection without the need to consult an HCP. If left untreated, it leads to further complications and morbidity (5). For most people, cold sores occur once or twice a year, but about 5-10% of people have more than five outbreaks a year.

Antiviral therapy shortens the duration of pain and discomfort, accelerates healing and discomfort, speeds healing and reduces viral shedding. To achieve optimal results, treatment must be started as soon as possible, ideally at the prodromal stage and no later than 48 hours after the appearance of the lesions (6). Potential delay in the start of treatment due to the need for an HCP visit and prescription, could therefore have a negative impact on the success of treatment.

Products containing acyclovir or penciclovir for the treatment of labial herpes were already released from the prescription requirement in many European countries for more than 20 to 30 years. Even though there

(1) WHO, Fact sheets "Antimicrobial resistance": https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance.

(2) WHO, Fact sheets "HIV drug resistance": https://www.who.int/news-room/fact-sheets/detail/hiv-drug-resistance (last accessed 6th June 2023)

(3) G.B. Elion. Acyclovir: discovery, mechanism of action and selectivity. J. Med. Virol. (1993)

(4) Consumer-oriented websites of the German Ministry of Health and IQWiG. Lippenherpes: Ursachen, Folgen, Behandlung | gesund.bund.de

(5) Gopinath D, Koe KH, Maharajan MK, Panda S. A Comprehensive Overview of Epidemiology, Pathogenesis and the Management of Herpes Labialis. Viruses. 2023 Jan 13;15(1):225. doi: 10.3390/v15010225.

(6) Leung AKC, Barankin B. Recent Pat Inflamm Allergy Drug Discov. 2017;11(2):107-113.

has been an increase in the use of acyclovir, penciclovir, and their prodrugs over the past two decades, this has not been accompanied by a detectable increase in the prevalence of antiviral resistant herpes simplex virus (HSV) in immunocompetent or immunocompromised populations (7)(8).

HSV strains that are resistant to acyclovir occur naturally at a very low frequency (~0.3% in immunocompetent and in < 10% immunocompromised patients). Prevalence of resistant strains has not increased over the more than 20 years that acyclovir has been available by prescription, or in the past decade since it has been available over-the-counter. A unique combination of virus-, host- and drug-related factors explains why resistance has not emerged in the general population.

In the field of cold sore OTC products, just tubes with a package size of 2 - 10 g are sold. Only a small amount of the drug is applied to the affected area. Topical products have the advantage that their active ingredient can be applied directly to the site of infection and the systemic availability of acyclovir when applied topically is very low. In a study on Zovirax cold sore cream, no acyclovir serum levels could be measured after repeated topical application (5 times daily for 4 consecutive days). The detection limit for acyclovir was < 0.01 µmol/l. Measurable acyclovir concentrations were detected in the urine, but these corresponded to less than 0.1 % of the amount of acyclovir applied to the skin. Overall, these values demonstrate a resorption of the acyclovir from Zovirax cold sore cream. However, their magnitude suggests that no systemic effect is to be expected (9).

(7) Bacon et al. CLINICAL MICROBIOLOGY REVIEWS, Jan. 2003, p. 114–128. Herpes Simplex Virus Resistance to Acyclovir and Penciclovir after Two Decades of Antiviral Therapy.

(8) Schalkwijk HH Snoeck R Andrei G. Acyclovir resistance in herpes simplex viruses: Prevalence and therapeutic alternatives. Biochem Pharmacol 2022. Vol 206, 115322 DOI: 10.1016/j.bcp.2022.115322.

(9) Zovirax SmPC, as of 05/2019

Is there a risk of resistance with clinical consequences in humans posed by molecules and dosage forms available in self-care?

Acyclovir and Penciclovir

The mechanism of action of penciclovir and acyclovir against HSV includes first a phosphorylation that is selectively catalysed by the viral TK and therefore takes place in HSV-infected cells only. The resulting penciclovir monophosphate is then further phosphorylated by cellular kinases to the corresponding triphosphate which inhibits specifically the viral DNA polymerase (Vere Hodge 1993) because of its broader substrate specificity compared to cellular DNA polymerases (Roizman 2001). As a consequence of the basically identical modes of action of acyclovir and penciclovir, mechanisms of resistance are also identical and based on mutations of the viral genes encoding for the TK and the DNA polymerase (Boyd 1993, Bacon et al. 2003); for reasons not yet known, acyclovir and penciclovir-resistant strains show different gene loci to be most frequently affected (Sarisky et al. 2001, Suzutani et al. 2003).

Three distinct classes of acyclovir-resistant TK mutant viruses have been identified in infected cell cultures and isolates from patients: these are TK negative mutants which completely lack TK activity (TK-), TK partial mutants which express reduced levels of TK (TKP), and TK altered mutants which are still able to phosphorylate thymidine but no more the analogue acyclovir (TKA) (Coen 1994). Approximately 95% of acyclovir-resistant HSV isolates are either TK- or TKP (Pottage and Kessler 1995), which due to the TK deficiency prevents the initial, virus-selective phosphorylation of acyclovir or penciclovir (Brown et al. 2002). However, the TK deficiency also results in a shortage of nucleoside triphosphates required for the replication of the viral DNA, at least in resting and neuronal host cells with no cellular TK activity (Roizman 2001). Consequently, reactivation from the latent phase in these kinds of mutants is inefficient and virulence significantly reduced (Coen 1996, Awan 1999, Bacon et al. 2003).

Acyclovir- and penciclovir-resistant strains with DNA polymerase mutations are very rare and have so far only been identified in immunocompromised patients (Pottage and Kessler 1995, Bacon et al. 2003). These show in general only a moderate decrease in virulence, replication in the periphery, and reactivation from the latent phase (Coen 1994, Pelosi et al. 1998).

TK- and TKP viruses are normally resistant to all nucleoside analogues that require viral TK for phosphorylation, i.e. acyclovir and penciclovir. In contrast, sensitivity to substances that act directly on the viral DNA polymerase is maintained, e.g. foscarnet and cidofovir. Resistant HSV strains with mutations in the DNA polymerase, selected by acyclovir, can also exhibit cross-resistance to substances that act directly on the DNA polymerase, such as e.g. foscarnet, cidofovir or vidarabin. Double mutants in the region of TK and the DNA polymerase have a broad spectrum of resistance to the majority of antiviral agents with HSV activity (Crumpacker 2001). Certain acyclovir-resistant TKA and DNA polymerase mutants may be sensitive or even hypersensitive to penciclovir (Boyd 1993, Chiou 1995, Pelosi et al. 1998). However, the clinical significance of such HSV mutants which are not cross resistant to penciclovir is uncertain. In practice, if resistance to acyclovir is suspected, a TK- or TKP virus is most likely to be involved and an antiviral treatment based on a different mode of action would be indicated.

Mixed isolates of wild-type viruses with resistant TK or DNA polymerase mutants complement each other regarding pathogenicity and acyclovir resistance in animal studies, which allows growth of otherwise sensitive viruses in the presence of virustatics [Coen 1994]. The heterogeneity of clinical isolates can thus also have a decisive influence on the pathogenicity and relative sensitivity to acyclovir and penciclovir and must be considered when the susceptibility of isolates is classified.

Post-Marketing Surveillance for Resistant HSV

Surveillance for acyclovir-resistant HSV has been undertaken in several countries since acyclovir was approved in the early 1980s.

Data published in 1998 from 2 surveys in the UK and US demonstrated that the prevalence of acyclovir-resistant HSV was stable when compared to earlier surveys (Reyes et al. 1997, Christophers et al. 1998). A UK survey of immunocompetent patients (most with genital herpes) revealed a prevalence of acyclovir-resistant HSV of 0.1-0.6%, with no apparent differences between treated and untreated groups (Christophers et al. 1998). Five of 1866 isolates were resistant to acyclovir (0.27%). In the same survey, 6.0% of isolates from severely immunocompromised patients were resistant to acyclovir. In the US survey (Reyes et al. 1997) the acyclovir resistance rate among HSV isolates from sexually transmitted disease patients was 0.1% (1/861) while the rate of resistance among the HIV positive patients was 5.6% (7/126). A further US survey focused on a HIV infected population and on isolates collected between April and December 1998, 6.5% (4/62) HSV isolates tested were resistant to acyclovir (Gnann et al. 1999).

A UK Company survey was conducted in General Practices across 6 geographical regions [SR14]. A total of 1297 patients with recurrent herpes labialis were sampled, 924 of which were culture positive. Susceptibility to penciclovir and to acyclovir was determined by the plaque reduction assay in MRC-5 cells and Vero cells, respectively. Only 1 isolate was resistant to both, acyclovir and penciclovir (0.1% resistant HSV, 1/924). These results demonstrate that the prevalence of acyclovir-resistant HSV type 1 is very low, even after 5 years of non-prescription use of acyclovir in the UK.

In a general population survey conducted in the US, (Bacon et al. 2002) reported that the prevalence of antiviral resistant HSV was very low. Among ca. 1000 isolates from individuals with an episode of recurrent herpes labialis not treated with topical antiviral agents 2 isolates had borderline resistance to acyclovir (0.2%) and all were susceptible to penciclovir.

Based on data in the US (Lipsitch et al. 2000) investigated the risk of a spread of acyclovir/penciclovir-resistant HSV-1 strains through topical treatment of recurrent herpes labialis in mathematical models in order (1) to estimate the extent to which antiviral treatment of herpes labialis contributes to a reduction in HSV-1 transmission and (2) to clarify the extent to which the selection pressure as a result of antiviral treatment promotes the spread of resistant HSV-1 strains in the population. As a result, the current extent of topical treatment of herpes labialis, has – if at all – only a slight influence on the transmission and prevalence of HSV-1 in the population. Even a considerable increase in antiviral treatment of recurrent herpes labialis, e.g. to 30% of all episodes, would reduce the transmission of HSV-1 only to a very modest extent (less than 5%).

Conclusion

Acyclovir and penciclovir show similar structures, modes of action, and induce similar rates of mutation resulting in viral resistance (Vere Hodge 1993).

Extensive use of acyclovir over about 20 years has not altered the prevalence of resistance to this antiviral (typically 0.1 – 0.6% of isolates) within the immunocompetent population (Bacon et al. 2003). Records of acyclovir-resistant HSV infections remained rare (Kost et al. 1993, Nyquist et al. 1994, Sande et al. 1998, Swetter et al. 1998) and no transmission of resistant HSV strains is known as yet (Patel and Barton 1995). Despite a marked increase in the use of nucleoside analogues during recent years, the development of HSV resistance is not a significant problem in clinical practice (Collins and Ellis 1993, Brown et al. 2002, Bacon et al. 2003).

The prevalence of penciclovir-resistant viruses is not expected to be any different from that of acyclovir-resistant HSV. Of particular relevance to this switch application is that there are very few reports associating topical acyclovir (or penciclovir) with resistant HSV in patients with recurrent herpes labialis despite the wide availability of topical acyclovir without prescription (Coen 1994).

Cases of clinically significant acyclovir-resistant HSV infections are limited almost exclusively to the immunocompromised population, especially to patients with AIDS (Erlich et al. 1989, Hill et al. 1991). Resistance rate in these patients ranges in the literature mostly from 2 to 10% (Reusser 1994, Christophers et al. 1998), also depending on the degree of immunosuppression and the duration of therapy (Englund

et al. 1990). It can reach up to 30% in patients with bone marrow transplantation and is therefore of clinical relevance (Englund et al. 1990, Chakrabarti et al. 2000, Morfin and Thouvenot 2003). Concern was raised that the widespread and considerably increased use of systemic and topical antiviral agents in this patient group could lead to a marked increase in resistant strains and to transmission of resistant viruses to other people (Pottage and Kessler 1995). Actually the extent to which immunosuppressed patients play an epidemiologically relevant role in the spread of resistant strains in the population cannot exactly be foreseen. However, there is currently no evidence even in immunocompromised subjects of any marked increase in the prevalence of resistant HSV strains (summarised in [Bacon et al. 2003]) and importantly penciclovir cream is not indicated for use in these patients.

Is the proposed risk minimization measure (i.e. prescription) the most effective mechanism?

A few antivirals are available without prescription in well-defined conditions when speed of treatment is key to avoid aggravation (e.g. labial herpes). Antivirals containing non-prescription medicines are usually available at a lower dosage than their prescription (Rx) equivalent or for shorter time treatments. These products have less units per packaging and treatment is stopped if not exerting a positive effect within a short time frame.

Self-care antivirals help people to take timely action and avoid aggravation of the condition. This time-sensitive availability reduces the burden on national healthcare systems, freeing doctors for more important pathologies, and prevents escalation of the infection or its transmission which is wise from a public health point of view.

Similarly to antifungals, back-switching those antivirals would add an heavy burden on already stretched national health funds and would delay the treatment of HSV where timeliness is particular crucial in this infection. This measure would be highly disproportionate in light of the extremely low incidence of resistance as described above.

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About

The Association of the European Self-Care Industry (AESGP) is a non-profit organisation which represents the manufacturers of non-prescription medicines, food supplements and self-care medical devices in Europe, an area also referred to as consumer healthcare products.

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