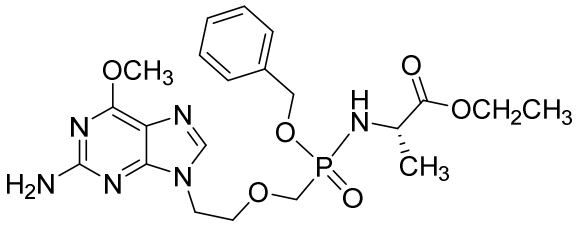
systems", *Recent Pat Drug Deliv Formul*., 2009, 3 (3) 193-205; and Sonal, G. et al. "Exploring Novel Approaches to Vaginal Drug Delivery", *Recent Patents on Drug Delivery and Formulation*, 2011, 5 (2) 82-94.

It is an object of the present invention to provide an effective pharmaceutical composition and treatment for HPV infection and related conditions such as HPV-induced neoplasia in a host in need thereof, including but not limited to cervical intraepithelial neoplasia (CIN), anal intraepithelial neoplasia (AIN), vulvar intraepithelial neoplasia (VIN), penile intraepithelial neoplasia (PIN), perianal intraepithelial neoplasia (PAIN) and vaginal intraepithelial neoplasia (VAIN).

SUMMARY

It has been discovered that an effective composition for the treatment of HPV infection and related diseases including HPV-induced neoplasia, such as cervical intraepithelial neoplasia, anal intraepithelial neoplasia, perianal intraepithelial neoplasia, penile intraepithelial neoplasia, vulvar intraepithelial neoplasia, and vaginal intraepithelial neoplasia, requires the combination of the selection of a number of aspects that work together to achieve the desired results. It was essential to select the right compound with advantageous lipophilic and tissue penetrating properties combined with a selected pharmaceutically acceptable salt optionally in an advantageous morphic form to achieve the long-sought ability to penetrate the epithelial stratified tissues in an effective amount to deliver the active agent. It required years of research to solve this problem, after many failures, to the benefit of patients globally suffering from interepithelial neoplasia that may become cancerous.

Specifically, it was discovered that the key compound is a specific salt of:

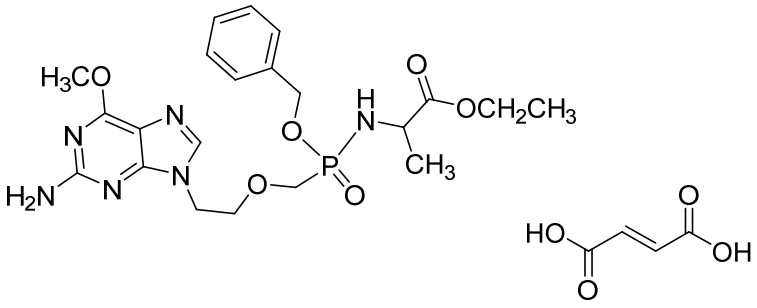


Compound I

In a non-limiting example, the advantageous salt (for example fumarate) of Compound I is used as a mixture of (*R,S*) and (*S,S*) diastereomers, wherein the first R/S designates the stereochemistry at the phosphorus atom and the second S is the stereochemistry of the carbon in the amino acid moiety (corresponding to the *L*-alanine residue having *S*-configuration). While any ratio of the diastereomers can be used that provides the desired results, the (*R,S*) diastereomer stands out. In other examples, the ratio is approximately 1:1 of the *R* to *S* enantiomer at the phosphorus atom. In examples, the compound is enantiomerically enriched with the *R* chirality at the phosphorus atom, wherein the amount of *R* by weight is for example, greater than about 50%, or equal to or greater than about 60%, 70%, 75%, 80%, or even 85% or more.

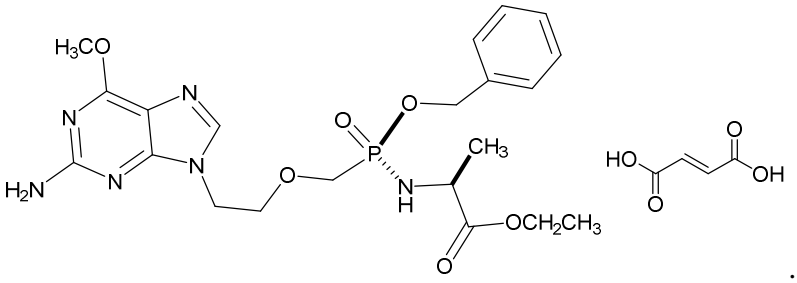
The S-stereoconfiguration at the chiral carbon corresponding to the natural amino acid configuration is advantageous in the present disclosure. In certain examples, the amount of S by weight is for example, greater than about 50%, or equal to or greater than about 60%, 70%,75%, 80%, or even 85% or more. In alternative examples, the compound is used with R-stereoconfiguration at the chiral carbon and wherein the R-stereoconfiguration is greater than about 50%, or equal to or greater than about 60%, 70%, 75%, 80%, or even 85% or more.

In one aspect, the present disclosure refers to a compound salt of the formula:



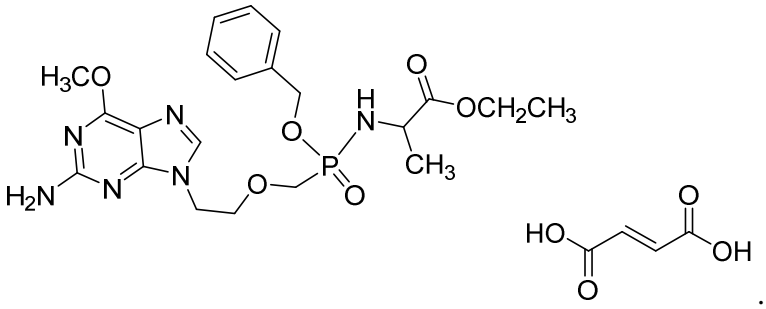
wherein the compound salt is isomerically enriched by greater than 50% by weight with R chirality at the phosphorus atom.

In one aspect, the present disclosure refers to a compound salt of the formula:

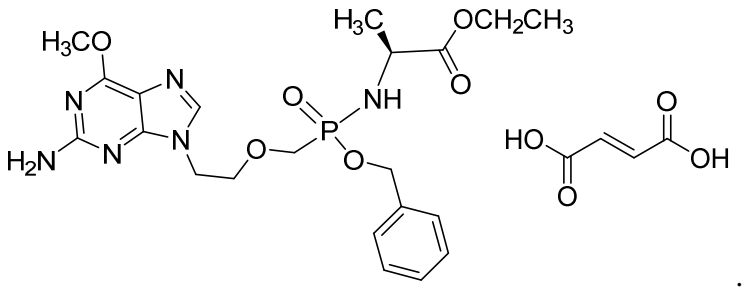


.

In one aspect, the present disclosure refers to a compound salt of the formula:



In one aspect, the present disclosure refers to a compound salt of the formula:



The enantiomerically pure (R_p,S_c, or simply "*R,S*") version of Compound I is a principal example. Unless described otherwise, an enantiomerically pure Compound II is at least 90% free of the opposite enantiomer. Surprisingly, the compound is an oil, not a solid, and thus would not have been selected as the active ingredient for the topical formulation. This is especially true because the racemic mixture or enantiomerically enriched *R,S* with *S,S* as a free base is a solid. Further, the *S,S* isomer has medium crystallinity as can be seen in FIG. 120. However, when formed as the fumarate salt, the *R,S* enantiomerically pure Compound I becomes a highly crystalline material and the most advantageous for intraepithelial topical administration. Thus, the monofumarate salt of Compound I exhibits unexpected stability, processability, and thus has therapeutic advantages over the free base Compound I.

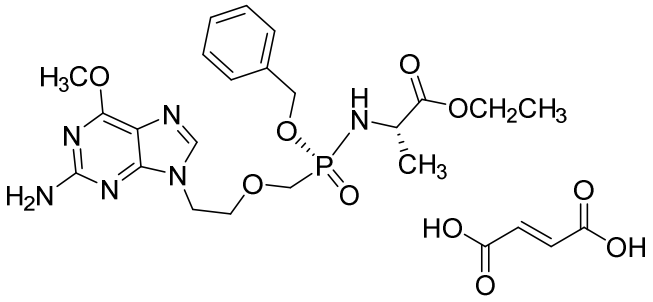
The monofumarate of the *R,S* isomer can be readily crystallized from isopropanol and heptanes. This morphic form is an anhydrate with a melting point of about 140°C (Example 15). This morphic form has been reproduced not only on milligram scale but also multigram scale.

While the *S,S* isomer was more easily handled as a free base, the monofumarate salt of the *S,S* isomer is polymorphic and has a lower melting point of about 105°C. Four morphic forms of

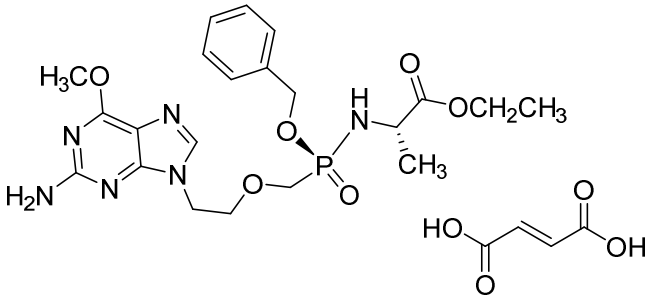
the *S,S* monofumarate salt were identified (Example 15). In certain experiments, dissociation of the *S,S* monofumarate into the hemifumarate was observed. Synthesis of this pattern was not reproducible when performed on larger scales.

It has been surprisingly discovered that certain pharmaceutical composition dosage forms prepared from Compound I monofumarate, and its morphic form Pattern 1, have advantageous properties. Tablets prepared from Compound I free base substantially degrade within one month at 40°C and 75% RH, but in contrast, tablets prepared from Compound I monofumarate experience far less degradation (Example 25), significantly increasing the shelf life.

Compound II as referred to herein and illustrated below is the enantiomerically enriched or pure example that has predominately R-stereochemistry at the phosphorus atom and S-stereochemistry at the amino acid carbon atom. In an enantiomerically pure form, Compound II exhibits superior stability properties over its stereoisomer, ethyl ((S)-((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(benzyloxy) phosphoryl)-L-alaninate monofumarate (Compound III). This is important for the success of the topical application to the cervix, vagina, vulva, perianal region, anus or penis.



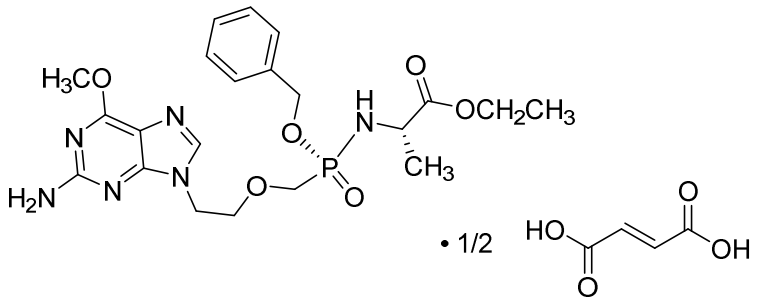
Compound II



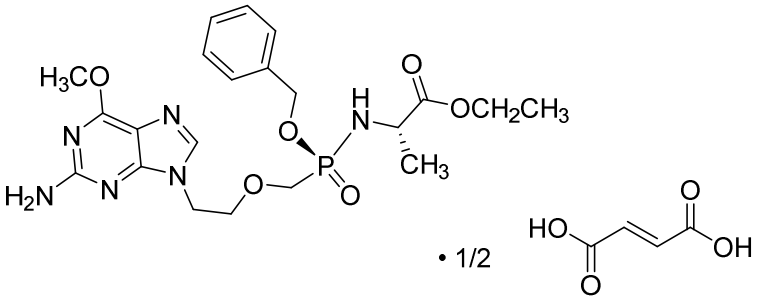
Compound III

Other advantageous salts of Compound I that have been discovered include the hemifumarate salts ethyl ((R)-((2-(2-amino-6-methoxy-9H-purin-9-

yl)ethoxy)methyl)(benzyloxy)phosphoryl)-L-alaninate hemifumarate (Compound IV) and ethyl ((S)-((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(benzyloxy)phosphoryl)-L-alaninate hemifumarate (Compound V).



Compound IV



Compound V

It has been discovered that Compound II has high tissue penetration and is surprisingly stable, crystalline, and nonhygroscopic. Compound II and its advantageous morphic form Pattern 1 can be used to treat HPV infection, or a disease associated with HPV infection, such as intraepithelial neoplasia, including but not limited to cervical intraepithelial neoplasia, anal intraepithelial neoplasia, vulvar intraepithelial neoplasia, penile intraepithelial neoplasia, perianal intraepithelial and vaginal intraepithelial neoplasia to prevent the transition to cancer.

There are many strains of HPV, some of which are strongly associated with the development of cancer and are known as high-risk strains. Compound I fumarate or Compound II can be used to treat the high-risk types of HPV, including HPV-16 and HPV-18. Thus, the present disclosure in certain examples provides Compound II and the isolated morphic form Compound II Patten 1, pharmaceutical compositions containing such compound, methods of treating an HPV infection or intraepithelial neoplasia related to HPV infection using the selected morphic form described herein, and methods of preparing such compound and morphic form.

In particular, it has been surprisingly discovered that the monofumarate salt of ethyl ((R)-((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(benzyloxy)phosphoryl)-L-alaninate (Compound II) has very high tissue penetration when administered topically to the target tissue. Topical administration avoids toxicity associated with systemic administration of the drug. Because precancerous and/or cancerous cells that are infected with HPV are several layers into the epithelium, the compound must have high penetration into the tissue to reach and treat these affected cells.

Compound I monofumarate has superior tissue permeation and penetration in both porcine and human vaginal tissues over ABI-1968, which failed in clinical trials despite also being a phosphonate ester of an acyclic purine nucleoside. Compound I monofumarate reaches concentrations of 40-85 ng/mL in vaginal tissue for a 0.1% dose. ABI-1968, even when used in a 3% dose does not reach even 15 ng/mL concentration (See FIG. 116). The significant improvement in tissue penetration, especially considering the decrease in dose, could not have been predicted in advance.

Compound II is surprisingly stable in comparison to its corresponding S_P isomer (Compound III). As shown in Example 7, Table 9, Compound II has a melting point of about 140°C$\pm$10°C, for example at 141.5°C, whereas Compound III has a melting point of about 100°C+10°C, for example 106.4°C. Compound II is also much more crystalline than Compound III, as can be seen from the XRPD data comparing the monofumarate salts of both compounds (See Example 13, Table 37 and FIG. 71 compared to Example 15, Table 40 and FIG. 77).

Careful selection of each example of the disclosure was crucial to achieve the desired results. One important example is the formulation. Topical formulations as used herein include semisolid dosage forms such as gels, creams, ointments, liquids or a solid dosage form. Nonlimiting examples of a solid dosage form includes a tablet, which can be inserted into the affected area.

It has been discovered that Compound I monofumarate, Compound II or Compound III can be prepared in a solid dosage form for topical administration. In some examples, the tablet formulation provides similar tissue penetration of the gel formulation (55-85 ng/mg for gel and 44-79 ng/mg for the tablet, FIG. 121).

High crystallinity can facilitate isolation and processing of pharmaceutical compounds. Compound II displays surprisingly little hygroscopicity compared to Compound III. When

exposed to a cycle of 40-0-95-0-45% relative humidity, Compound II retains about 0.25% water content, and the XRPD pattern does not change (Example 21, Table 46). Exposed to the same conditions, Compound III retains about 10% water content, a 40-fold increase. These conditions also cause the XRPD pattern to lose one of the peaks, indicating that Compound III is changing morphic forms in response to humidity changes. The hygroscopicity and stability benefits of Compound II over Compound III are surprising and could not be predicted in advance.

Compound II Pattern 1 can be produced, for example, by recrystallizing Compound II (Example 13, Table 37) and equilibration in a suitable solvent (Example 22). In certain examples, Compound II can be dissolved in an alcoholic solvent, for example isopropanol, and crystallized as Pattern 1 by the addition of an aliphatic solvent, for example heptane. In certain examples, Compound II can be dissolved in an alcoholic solvent, for example, ethanol, and crystallized as Pattern 1 by the addition of an aliphatic solvent, for example heptane. Compound II Pattern I may also be prepared by equilibration in isopropanol, heptane, water, acetone, isopropanol:heptane (3:10), isopropanol:MTBE (1:3), and ethyl acetate: toluene (1:3).

Compound III Pattern I can be prepared in multiple steps (see Example 15). First, Compound III free base was dissolved in isopropanol. One equivalent of fumaric acid was added, inducing precipitation. After addition of heptanes, the mixture was stirred at elevated temperature, for example 50 °C, for 20 hours then cooled. A further 0.2 equivalent of fumaric acid was added along with heptane and the mixture stirred at elevated temperature for at least about 13 hours. The suspension was then cooled slowly until reaching less than about 5 °C and stirred at that temperature for at least about 2 days. The resulting solid, Compound III Pattern I, was collected by filtration.

Compound I (i.e., a mixture of R and S enantiomers at the phosphorus atom and the S stereoisomer at the amino acid carbon) monofumarate Pattern 1 can be produced, for example, by recrystallizing Compound I monofumarate (Example 12, Table 31), equilibration of Compound I monofumarate in a suitable solvent, or crystallization by slow evaporation of solvent (Example 12, Table 32). In certain examples, Compound I monofumarate can be dissolved in an alcoholic solvent, for example isopropanol, and crystallized as Pattern 1 by the addition of an aliphatic solvent, for example heptanes. In certain examples, Compound I monofumarate can be dissolved in an alcoholic solvent, for example, isopropanol, and crystallized as Pattern 1 by the

addition of an ethereal solvent, for example methyl tert-butyl ether. In certain examples, Compound I monofumarate Pattern 1 can be produced by equilibration in a mixture of an ethereal solvent, for example tetrahydrofuran, and an aliphatic solvent, for example heptane. In certain examples, Compound I monofumarate Pattern 1 can be produced by crystallization by slow evaporation of solvent at room temperature. Suitable solvents for slow evaporation crystallization of Compound I monofumarate Pattern 1 include but are not limited to, acetone, methyl ethyl ketone, ethyl acetate, methanol, ethanol, isopropanol, and tetrahydrofuran. In certain examples, Compound I monofumarate Pattern 1 is characterized by an XRPD pattern comprising at least three 2theta values selected from 6.0±0.2°, 8.9±0.2°, 9.6±0.2°, 11.1±0.2°, 11.9±0.2°, 14.8±0.2°, 15.3±0.2°, 18.1±0.2°, 20.2±0.2°, 23.1±0.2°, 25.2±0.2°, and 27.0±0.2° (see Example 7).

Other morphic forms of Compound I monofumarate were prepared, including Pattern 2, Pattern 3, and Pattern 4. However, these morphic forms are sometimes unstable and result in the hemifumarate (a mixture of Compound IV and Compound V), even when prepared from the monofumarate.

Recrystallization of Compound I monofumarate in methyl ethyl ketone; acetone; acetone and heptanes; methyl ethyl ketone and heptanes; and ethanol and methyl tertbutyl ether all result in the hemifumarate Pattern 2. The ratio of Compound I as a free base to fumarate measured by ^{1}H NMR is about 1:0.5, for example 1:0.52. In one example, Pattern 2 is characterized by an XRPD pattern comprising at least three 2theta values selected from 4.3±0.2°, 6.2±0.2°, 9.0±0.2°, 13.0±0.2°, 17.7±0.2°, 18.7±0.2°, and 25.3±0.2° (see Example 12).

Recrystallization of Compound I monofumarate in acetonitrile or acetonitrile and water provides the hemifumarate Pattern 3. The ratio of Compound I as a free base to fumarate measured by ^{1}H NMR after isolation by filtration is about 1:0.95, but after washing with water the ratio decreases to about 1:0.76. In one example, Pattern 3 is characterized by an XRPD pattern comprising at least three 2theta values selected from 3.5±0.2°, 5.1±0.2°, 6.2±0.2°, 6.9±0.2°, 10.2±0.2°, 15.3±0.2°, 17.6±0.2°, 21.2±0.2°, and 28.9±0.2° (see Example 12). Recrystallization of Compound I monofumarate in acetone and toluene provided the hemifumarate Pattern 4. The ratio of Compound I as a free base to fumarate measured by ^{1}H NMR is about 1:0.7, for example 1:0.69. In one example, Pattern 4 is characterized by an XRPD pattern comprising at least three 2theta

values selected from 4.0±0.2°, 6.0±0.2°, 11.8±0.2°, 13.2±0.2°, 14.8±0.2°, 17.7±0.2°, 20.4±0.2°, and 25.2±0.2° (See Example 12). Due to the superior properties of the monofumarate over the hemifumarate, Compound I monofumarate Pattern 1 was selected for further study due to its surprising stability and crystallinity.

In non-limiting examples, a method for the treatment of HPV-induced intraepithelial neoplasia is provided that includes administering an effective amount of one or a combination of the active compounds as described herein in a topical formulation that is sufficient to treat the neoplasia.

In an example, a formulation for the treatment of intraepithelial neoplasia is a dosage form containing of from 0.005 mg to 50 mg, from 0.05 mg to 40 mg, from 0.1 mg to 30 mg, from 0.5 mg to 20 mg, from 1 mg to 20 mg, from 1 mg to 15 mg, from 1 mg to 10 mg of Compound I monofumarate, Compound II or Compound III.

In certain examples, a formulation for the treatment of intraepithelial neoplasia is a dosage form containing of from about 0.001 to about 20 mg, from about 0.005 to about 10 mg, from about 0.01 mg to about 5 mg, from about 0.03 mg to about 1 mg, from about 0.05 mg to about 0.3 mg, from about 0.03 mg to about 0.07 mg, from about 0.05 mg to about 0.15 mg, or from about 0.15 mg to about 0.45 mg of Compound I monofumarate, Compound II or Compound III.

In certain examples, a formula for the treatment of intraepithelial neoplasia is a dosage form containing from about 0.001 milligrams to about 0.005 milligrams, from about 0.005 milligrams to about 0.01 milligram, from about 0.01 milligram to about 0.03 milligram, from about 0.03 milligrams to about 0.25 milligrams, from about 0.20 milligrams to about 0.5 milligrams, from about 0.4 milligrams to about 1 milligram, from about 0.75 milligram to about 3 milligrams, from about 1 milligram to about 10 milligrams, from about or 5 milligrams to about 20 milligrams. In certain examples, a formulation for the treatment of intraepithelial neoplasia is a dosage form contains about or at least 0.005, 0.01, 0.03, 0.05, 0.1 mg, 0.3 mg. 0.5 mg, 0.7 mg, 1 mg, 1.5 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45mg or 50 mg of Compound I monofumarate, Compound II or Compound III.

A particular dosage is 0.05 mg, 0.1 mg, 0.2 mg, or 0.3 mg of Compound I monofumarate, Compound II or Compound III. In certain examples, the 0.05 mg, 0.1 mg, 0.2 mg, or 0.3 mg dosage of Compound I monofumarate, Compound II or Compound III is administered once, twice,

or three times per week as needed. In certain examples the 0.05 mg dosage of Compound I monofumarate, Compound II or Compound III is administered for the prescribed time instructed by the healthcare provider, including daily dosing.

In certain examples, the topical formulation is administered twice a day, once a day, or several days a week (such as 2 or 3 days a week), as long as necessary to achieve the desired results. In certain examples, the topical formulation is administered on a weekly schedule for one, two, three, four, five, six or more weeks. In certain examples, the topical formulation is administered on a schedule of three dosages a week for two, three four, five or six weeks.

In certain examples, the compound can be administered in one or more therapeutic cycles comprising a treatment cycle and a rest cycle, wherein the treatment cycle comprises administering the compound as described herein, followed by a rest cycle (comprising a period of no treatment) before the next treatment cycle. In certain examples, the rest cycle is from about one day to about six months. In certain examples the rest cycle is one, two, three, four, five, six, seven, eight or more weeks before the next treatment cycle. In certain examples, multiple therapeutic cycles are administered, for example one, two, three, four, five, or six therapeutic cycles.

Dosage forms which do not adhere well to the target site may be dislodged, interfering with treatment. Dosage forms have been discovered that adhere to the target site and dissolve rapidly in low fluid volumes. Adhesion to the target site also prevents exposure to non-target tissues, which may limit toxicity, unwanted systemic exposure, and side effects. Dosage forms which soften, break down, and/or disintegrate quickly in low fluid volumes are advantageous to cause a rapid release of the active compound to the target tissue. Dosage forms that disintegrate in, for example, less than about 50 µL, less than about 100 µL, less than about 125 µL, less than about 150 µL, less than about 175 µL, less than about 200 µL, less than about 250 µL, less than about 500 µL, less than about 1 mL, or less than about 2 mL fluid facilitate drug penetration into the target site.

In certain examples, the dosage form is a semisolid such as a gel or cream. In certain examples, the dosage form is a tablet. In certain examples, the dosage form disintegrates in about one to about ten seconds. In certain examples, the dosage form disintegrates in about ten seconds to one minute, in certain examples, the dosage form disintegrates in about one

minute to about one hour. In certain examples, the dosage form disintegrates in one to six hours.

The physical dimensions of the dosage form can impact the effectiveness of the dosage form. A tablet that is thinner provides a greater surface area to volume ratio and may degrade quicker and cover the target area better. In certain examples the dosage form is less than 3 millimeters thick in its smallest dimension.

The formulation of the dosage form is very important for adequate administration of the active agent into the intraepithelial tissue. The formulation for example, can be prepared for use as a tablet, a reconstituted powder, a dry powder, a semi solid dosage form, a film or a pessary (i.e., a vaginal suppository).

Tablet formulation should display the properties of mucoadhesion and substantivity and include excipients that have solubilizing, erosion-generating (for disintegration), porosity (for water uptake) and viscosity enhancing (to keep the drug at the target site) properties.

Examples of excipients that will cause rapid disintegration of a solid dosage form to cover the cervix, anal, penile, perianal, vulvar, or vaginal areas include, but are not limited to mannitol, microcrystalline cellulose, lactose, sucrose, calcium phosphate, sodium phosphate, sodium bicarbonate, citric acid, maleic acid, adipic acid or fumaric acid. Examples of excipients that can enhance disintegration and coverage of the affected area include but are not limited to sodium starch glycollate, pregelatinized starch, crospovidone and croscarmellose sodium. Mucoadhesive excipients that are useful in the present disclosure include but are not limited to microcrystalline cellulose, polycarbophil, hydroxymethyl cellulose, hypromellose, hydroxypropyl cellulose, and PVP.

A nonlimiting example of a tablet formulation includes, but is not limited to, microcrystalline cellulose, crospovidone, magnesium stearate, silicon dioxide, polyethylene oxide and mannitol. Another non-limiting example of a tablet formulation has microcrystalline cellulose, magnesium stearate and mannitol.

Alternative formulations are reconstituted powders or dry powders. These formulations can include excipients described above and in certain examples xanthan gum can be added. As a non-limiting example, a dry powder formulation can include, but is not limited to, xanthan gum, mannitol, silicon dioxide and sodium benzoate.

Semi solid dosage forms may include, for example, a mucoadhesive polymer, a solubility/penetration enhancer, a lipophilic solubilizer and a penetration enhancer. The mucoadhesive polymer, for example, may be, but is not limited to, a carbomer, polyethylene glycol, crospovidone, hypromellose, polycarbophil and/or hydroxyethyl cellulose. The solubility/penetration enhancer can be, for example, but not limited to, a mixture of polyoxyl 6 stearate Type I, ethylene glycol stearates and polyoxy 32 stearate Type I, cetyl alcohol, stearyl alcohol, polysorbate 80, sodium lauryl sulphate, mono and di-glycerides, sorbitan monostearate, glyceryl isostearate, polyoxy 15 hydroxystearate, poly15 hydroxystearate, polyoxy 40 hydrogenated castor oil, octyl dodecanol, and/or soybean lecithin. Lipophilic solubilizers include, but are not limited to light mineral oil, mineral oil, white wax and silicone fluid. Penetration enhancers include but are not limited to propylene glycol, transcutol, oleic acid, isopropyl myristate, propylene glycol glycerol monooleate, propylene glycol monocaprylate, PEG-8 Bees wax, cetyl alcohol, stearic acid, cetyl palmitate and/or cetostearyl alcohol.

A non-limiting example of a semi-solid formulation includes, for example, a carbomer, propylene glycol, sorbic acid, EDTA and water. Another non-limiting example of a semi solid formulation includes a carbomer, mineral oil, a mixture of polyoxy 6 stearate Type I, ethylene glycol stearate, polyoxy 32 stearate Type I, parabens, propylene glycol, EDTA and/or water.

Films can be produced, for example, with, but not limited to, hypromellose, polyethylene glycol, polymethacrylates, microcrystalline cellulose, xanthan gum, guar gum and/or polyvinylpyrrolidone.

A pessary (vaginal suppository) can be formulated with, for example but not limited to, hard fat (such as Ovucire, Witepsol, Supposi-Base), polyethylene glycol, macrogols, cocoa butter and glycerol. A non-limiting example of a pessary can be made from Witepsol H 15 or Ovucire WL 3264.

Therefore, the present disclosure includes at least the following examples:

(i) Compound I monofumarate;

(ii) Compound II;

(iii) Compound III;

(iv) Compound IV;

(v) Compound V;

(xxiii) The topical formulation of (xiv) in the form of a reconstituted powder;

(xxiv) The topical formulation of (xiv) in the form of a dry powder dosage form;

(xxv) The topical formulation of (xiv) in the form of a film;

(xxvi) The topical formulation of (xiv) in the form of a pessary;

(xxvii) Advantageous dosage forms of (xv)-(xxvi) for delivery to the cervix, vagina, vulva, penis, perianal region, and/or anus;

(xxviii) A method to treat an HPV-induced infection or an associated condition, including but not limited to intraepithelial neoplasia such as cervical, vaginal, vulvar, perianal, anal or penile, comprising administering to a host in need thereof an effective amount of a compound, morphic form, or pharmaceutical composition of any one of examples above to a host in need thereof;

(xxix) Use of any of the examples above in the manufacture of a medicament for the treatment of HPV infection or an associated condition, including but not limited to intraepithelial neoplasia such as cervical, penile, vulvar, perianal, anal or vaginal, in a host in need thereof;

(xxx) Examples (i)-(xxvii) for use to treat HPV infection or an associated condition, including but not limited to intraepithelial neoplasia, such as cervical, penile, vulvar, perianal, anal or vaginal, in a host in need thereof;

(xxxi) Any one of above examples, wherein the host is a human;

(xxxii) Any of the topical formulations described above, for the treatment of intraepithelial neoplasia that provides a dosage form containing of from 0.005 mg to 50 mg, from 0.05 mg to 40 mg, from 0.1 mg to 30 mg, from 0.05 to 0.3 mg, from 0.5 mg to 20 mg, from 1 mg to 20 mg, from 1 mg to 15 mg, from 1 mg to 10 mg of a compound of examples (i)-(v) and in certain examples about or at least 0.005, 0.01, 0.03, 0.05, 0.1 mg, 0.3 mg. 0.5 mg, 0.7 mg, 1 mg, 1.5 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45mg or 50 mg;

(xxxiii) Any of the topical formulations described above, for the treatment of intraepithelial neoplasia that provides a dosage form containing from about 0.001 to about 20 mg, from about 0.005 to about 10 mg, from about 0.01 mg to about 5 mg, from about 0.03 mg to about 1 mg, from about 0.05 mg to about 0.3 mg, from about 0.03 mg to about 0.07 mg,

from about 0.05 to about 0.15 mg, or from about 0.15 mg to about 0.45 mg of a compound of examples (i)-(v).

(xxxiv) The topical formulation of examples (xiv) to (xxvii) administered twice a day, once a day, or several days a week (such as 2 or 3 days a week), or as long as necessary to achieve the desired results;

(xxxv) The topical formulation of examples (xiv) to (xxvii) that are administered on a weekly schedule for one, two, three, four, five, six or more weeks;

(xxxvi) The method of (xxviii), further including applying a lubricant to the dosage form or epithelial tissue before inserting the dosage form in the affected area;

(xxxvii) The method of (xxxvi), wherein the lubricant is selected from water, a glycerol based lubricant and a hydroxyethylcellulose-based lubricant; and

(xxxviii) Process for the preparation of the topical formulations of examples of (xiv) to (xxviii);

(xxxix) A method to treat an HPV-induced infection or an associated condition, including but not limited to intraepithelial neoplasia such as cervical, penile, vulvar, perianal, anal or vaginal, comprising administering an effective amount of examples (i)-(xxii) to a host in need thereof, in combination with surgical treatment of the target tissue before, during or after administration of the compound;

(xl) The method of (xxxix) comprising a surgical treatment of the target tissue followed by administering an effective amount of examples (i)-(xxii) to a host in need thereof;

(xli) The method of (xxxiv) comprising administering an effective amount of examples (i)-(xxii) to a host in need thereof, followed by surgical treatment of the target tissue;

(xlii) The method of (xxxiv) comprising administering an effective amount of examples (i)-(xxii) to a host in need thereof, around or at approximately the same time as surgical treatment of the target tissue;

(xliii) The method of examples (xxxiv)-(xxxvii) wherein the surgical treatment of the target tissue is excision;

(xliv) The method of examples (xxxiv)-(xxxvii) wherein the surgical treatment of the target tissue is ablation;