



Public Health
England

Protecting and improving the nation's health

Updated guidelines on post exposure prophylaxis (PEP) for varicella/shingles

June 2019

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Changes from the previous guidelines

June 2019

Updated title to reflect that this includes VZIG and anti-viral guidance.

Antivirals recommended for immunosuppressed individuals, except for those where oral aciclovir /valaciclovir may be contraindicated.

VZIG recommended for those with a significant exposure before 20 weeks of pregnancy.

Preferential use of anti-virals rather than VZIG as post-exposure prophylaxis (PEP) for pregnant women exposed from 20 weeks although the decision on choice of PEP should take into account patient and health professional preference as well as the ability to offer and provide PEP in a timely manner.

August 2018

Strengthening guidance on use of aciclovir in susceptible women with a significant exposure from weeks 20 of pregnancy from 'consider to 'recommend'.

Use of valaciclovir as an alternative to aciclovir in women exposed from weeks 20 of pregnancy.

Restriction of VZIG extended to include all immunosuppressed individuals, except for those where oral aciclovir/valaciclovir may be contraindicated.

Executive summary

Chicken pox (varicella) infection in neonates, immunosuppressed individuals and pregnant women can result in severe and even life-threatening varicella disease. Post-exposure prophylaxis (PEP) is recommended to attenuate disease and reduce the risk of complications such as pneumonitis, rather than to prevent infection in these at-risk individuals.

In response to a severe national shortage of varicella zoster immunoglobulin (VZIG) due to manufacturing issues from the sole UK supplier in July 2018, an expert working group convened by the Immunisation Division at PHE reviewed the evidence on the safety and efficacy of antiviral agents as an alternative for post-exposure prophylaxis (PEP). Restrictions on the use of VZIG were implemented to prioritise stock for the most vulnerable groups whilst supplies were limited and antivirals were advised as suitable alternatives in immunosuppressed contacts and pregnant women exposed from 20 weeks. A series of evaluations have commenced to gather further evidence on the efficacy of antivirals as PEP in pregnant women and immunosuppressed groups as well as an acceptability survey of health professionals and patients on antiviral use.

In April 2019, the expert working group reconvened to review the VZIG supply situation and available data from the ongoing evaluations. The group considered a number of factors relating to current and future immunoglobulin supply in informing their advice. This included:

- (1) The fact that VZIG is currently procured by PHE from a sole supplier and the limited availability of a suitable alternative IG product. Interruptions in supply have occurred in the past and this remains a potential risk in the future
- (2) Global supplies of a range of immunoglobulin products have been limited in recent years and supplies are likely to remain constrained in the future

Therefore, the ability to identify suitable alternative products not derived from blood is important.

In light of the resumption of VZIG supplies and available evidence on safety and efficacy of antivirals, updated interim guidance on PEP has been published.

The key recommendations are:

Pregnant Women

- 1) VZIG should be issued to VZ antibody negative pregnant contacts exposed in the first 20 weeks of pregnancy, ie up to and including 20+0 weeks. There is limited evidence on the effectiveness of oral antiviral agents at preventing congenital varicella.
- 2) For susceptible women exposed after 20 weeks, ie from 20+1 weeks to delivery, either VZIG or oral aciclovir at 800mg 4 times a day from days 7 to 14 after exposure is recommended. Valaciclovir 1000mg 3 times a day from days 7 to 14 after exposure can be used as a suitable alternative. This recommendation is based on the existing evidence on the safety of aciclovir in the second and third trimesters of pregnancy, the efficacy of aciclovir in preventing clinical chickenpox in healthy and immunosuppressed contacts and relative sub-optimal efficacy of VZIG as PEP in pregnant women.

All pregnant women who are exposed to chickenpox or shingles should be assessed for susceptibility as described in national guidelines. ^[1] If there is no history of chickenpox, women should be tested for varicella antibodies using a quantitative assay with <100mIU/ml denoted susceptibility. The decision on choice of PEP for women exposed from 20 weeks of pregnancy should take into account patient and health professional preference as well as the ability to offer and provide PEP in a timely manner.

Immunosuppressed individuals

Based on the current evidence, oral aciclovir or valaciclovir is recommended for susceptible immunosuppressed individuals unless there are significant concerns of renal toxicity or malabsorption.

Neonates

There are no changes to the guidance¹ for neonates and VZIG continues to be recommended.

PHE is keeping the situation under constant review. This interim guidance will remain in place until further notice.

1. Background

Public Health England (PHE) guidelines^[1] recommend post exposure prophylaxis (PEP) with Varicella Zoster Immunoglobulin (VZIG) for individuals at high risk of severe chickenpox who are known to be susceptible. These groups are immunosuppressed individuals, neonates in the first week of life, and pregnant women. For those not meeting the criteria for VZIG (based on level of exposure; antibody status and/or level of risk of severe disease) antivirals were advised.

In response to a significant national shortage of VZIG, due to manufacturing issues from the sole UK supplier, urgent restrictions were put in place on the issuing of VZIG from July 2018. Based on an urgent review by an expert working group convened by PHE, from August 2018, it was recommended that VZIG be restricted to susceptible pregnant women exposed in the first 20 weeks and neonates. For susceptible immunosuppressed individuals (as defined in 2016 PHE Guidelines^[1]) and pregnant women exposed from 20 weeks, antivirals (either aciclovir or valaciclovir) were recommended unless there was a specific contraindication.

In April 2019, the expert working group reconvened to review the supply situation and available data from ongoing studies evaluating the efficacy of antivirals as PEP. In light of the resumption of VZIG supplies, the existing restrictions were reviewed.

This document summarises the current advice of the expert working group on the use of VZIG and antivirals as PEP. The group considered a number of factors relating to current and future immunoglobulin supply in informing their advice. This included:

1. The fact that VZIG is currently procured by PHE from a sole supplier and the limited availability of a suitable alternative IG product. Interruptions in supply have occurred in the past and this remains a potential risk in the future.
2. Global supplies of a range of immunoglobulin products have been limited in recent years and supplies are likely to remain constrained in the future. Therefore, the ability to identify suitable alternative products not derived from blood is important.

2. Immunosuppressed individuals

All immunosuppressed individuals as defined in Chapter 6 (Immunisation against infectious disease – the Green Book) ^[10] are at risk of severe chickenpox and should be assessed for the need for prophylaxis following a significant exposure. However, many adults and older children with immunosuppression will have immunity due to past infection and therefore a risk assessment of the degree of immunosuppression as described in the PHE guidelines^[1] should be undertaken to inform the need for VZV IgG testing and/or post-exposure prophylaxis.

Efficacy and safety of VZIG and aciclovir in immunosuppressed individuals

Efficacy of VZIG in preventing severe complications of chickenpox in immunosuppressed individuals was demonstrated in a follow up of 122 children in high risk groups who received VZIG following an exposure, including 80 seronegative children.^[11] Of the 27 exposed in the household, 18 seroconverted (14 with symptoms). Seroconversion in hospital exposures was considerably lower (6 of 43 with 3 developing symptoms). Of the 17 symptomatic cases, only 2 were severe but in both of these VZIG was administered outside of the optimal window.

Efficacy of aciclovir for post exposure prophylaxis in immunocompromised individuals has been evaluated in a small number of retrospective studies. The findings from these have varied from reporting no breakthrough varicella infections following aciclovir while others report a rate of 3–22%.^[12] In a retrospective observational study evaluating the effectiveness of aciclovir post exposure prophylaxis in 141 contacts exposed to varicella in a paediatric setting between 2000 and 2007 in a Japanese hospital, the rate of secondary infection was 2.1% in all contacts and 3.1% for immunocompromised contacts. ^[13] This compares with a secondary infection rate of 18% in those not receiving any post exposure prophylaxis (RR 8.5 (95%CI: 1.6-45.9)).

There is an ongoing UK observational study of immunosuppressed children with underlying haematology or oncology diagnoses who are exposed to VZV and require PEP. As practice is variable across the UK, a proportion of these children receive VZIG while others receive acyclovir. Of the 73 patients recruited as of 1st April 2019, interim analysis has indicated that aciclovir is at least equivalent, if not better than VZIG with respect to preventing clinical chickenpox (unpublished data).

With respect to safety, aciclovir has a good safety profile for immunosuppressed individuals and this compares with the potential (albeit low) risk from VZIG, as a blood product.

The 2002 RCPCH guidelines for the ‘Immunisation of the Immunocompromised Child’ recommended that aciclovir or VZIG can be offered to these individuals.^[7] As such, it has been routine practice for in approximately 50% of paediatric oncology centres across the UK to preferentially use antivirals for PEP in their paediatric population.

Recommendation for Immunosuppressed Contacts

Based on the current evidence, oral aciclovir is the first choice of PEP for susceptible immunosuppressed individuals.

Immunosuppressed individuals who are exposed to chickenpox or shingles should still be assessed for susceptibility as described in the [national guidelines](#).^[1] For those identified as susceptible, and who would otherwise be offered VZIG, antivirals (oral aciclovir or valaciclovir) should be given from day 7 to day 14 after exposure. The day of exposure is defined as the date of the rash if the index is a household contact and date of first or only contact if the exposure is on multiple or single occasion(s) respectively.

If the patient presents after day 7 of exposure, a 7 day course of antivirals can be started up to day 14 after exposure, if necessary.

The dose of aciclovir is based on the Children’s BNF^[14] for the attenuation of infection if VZIG is not indicated (see table). There is limited evidence for dosing for valaciclovir prophylaxis but given the improved bioavailability, fewer daily doses and better side effect profile, valaciclovir may be preferred. The dosage of valaciclovir is based on the therapeutic dose for chickenpox.

| | Oral Aciclovir | Oral Valaciclovir |
|-----------------------------------|---|--|
| Children under 2 years age | 10mg/kg 4 times daily, days 7 to 14 after exposure | Not recommended |
| Children 2-17 years of age | 10mg/kg (up to a maximum of 800mg), 4 times daily days 7 to 14 after exposure | 20 mg/kg (up to a maximum 1000mg) 3 times daily, days 7 to 14 after exposure |
| Adults | 800mg 4 times daily, from days 7 to 14 after exposure | 1000mg 3 times daily, from days 7 to 14 after exposure |

Individuals on long term aciclovir/valaciclovir prophylaxis, for example post-haematopoietic stem cell transplant may require their dose of aciclovir to be temporarily increased to the dosage as given in the table on previous page.

Reason for starting antivirals at day 7 after exposure

In a study evaluating the comparative effectiveness of 7 days course of aciclovir given either immediately after exposure or starting at day 7 after exposure to healthy children, the incidence and severity of varicella infection was significantly higher in those given aciclovir immediately (10/13 (77%) who received aciclovir immediately developed clinical varicella compared with 3/14 (21%) who started aciclovir at day 7).^[8]

A 7 day post exposure exposure prophylaxis course of aciclovir/valaciclovir is therefore recommended to start from day 7 after exposure.

Immunosuppressed patients presenting with chickenpox

If, despite having taken prophylactic aciclovir/valaciclovir, an immunosuppressed patient presents with a chickenpox rash, they should be changed onto a therapeutic dose. starting from the day of onset of the rash. If severe chickenpox develops, the patient may need to be hospitalised and given IV aciclovir.

Off label use of aciclovir and valaciclovir

Although aciclovir and valaciclovir are not licensed for post-exposure prophylaxis for chickenpox, their use in the treatment of chickenpox is well established. Clinicians are able to prescribe medicines outside the terms of the licence when it is in the best interest of the patient on the basis of available evidence. This evidence has been considered and recommended by the PHE convened expert working group (see Appendix 1 for membership).

Further advice on off-label prescribing is on the MHRA website:

www.gov.uk/drug-safety-update/off-label-or-unlicensed-use-of-medicines-prescribers-responsibilities#prescribing-in-a-patients-best-interests

When current practice supports the use of a medicine outside the terms of its licence, the MHRA advise that it may not be necessary to draw attention to this when seeking consent from patients. However, it is good practice to give as much information as patients or carers require or which they may see as relevant.

Contraindications and precautions to aciclovir and valaciclovir

In individuals with renal impairment or intestinal malabsorption, for example inflammatory bowel disease, VZIG may be considered. The dose of aciclovir may need to be adjusted in patients with renal impairment. See the British National Formulary (BNF) for more information.

Subsequent exposure to chickenpox or shingles

Patients who have a second or further exposures, should be risk assessed in line with **national guidelines**.^[1] Given the rates of seroconversion with both VZIG and aciclovir, patients should have a repeat VZV antibody test prior to considering a course of aciclovir/valaciclovir. Given the short half life of aciclovir/valaciclovir compared with VZIG, if there is a second exposure immediately after a course of antivirals, a second risk assessment and course should be given in the same way starting 7 days after the subsequent exposure.

3. Pregnant contacts

Why PEP is recommended for pregnant women

Chickenpox infection during the first 20 weeks of pregnancy can lead to fetal varicella syndrome, which includes microcephaly, cataracts, growth retardation limb hypoplasia, and skin scarring. Chickenpox can cause severe maternal disease and this risk is greatest in the second or early in the third trimester.

The rationale for PEP in pregnant women is twofold: reduction in severity of maternal disease and theoretical reduction in the risk of fetal infection for women contracting varicella in the first 20 weeks of pregnancy. In late pregnancy, PEP may also reduce the risk of neonatal infection. However, given the risks of severe neonatal varicella in the first week of life, VZIG is also given to infants born within 7 days of onset of maternal varicella.

In the absence of PEP, risk of developing varicella in susceptible contacts is high with 13/18 72% of seronegative pregnant women developing varicella following a significant exposure.^[5]

Safety of PEP in pregnancy

VZIG is a concentrated preparation of antibodies against chickenpox (varicella) derived from healthy non-UK blood donors. As with any other blood product, although screened for HIV, Hepatitis B and C, there remains a very low risk of transfusion transmitted infections.

Although oral aciclovir and valaciclovir (prodrug of aciclovir) are not licensed in pregnancy, there is extensive evidence of safety in pregnancy, including from 2 large registries of infants whose mothers were exposed to aciclovir in pregnancy. Aciclovir is also recommended for treatment of chickenpox in women who are more than 20 weeks pregnant. From follow up across 24 countries between 1984 -1999 of over 1200 pregnancies that received either oral or IV aciclovir across all stages of pregnancy, no unusual defects or patterns of defects were observed.^[4] In a Danish national cohort study of 1804 exposures to antiviral agents (aciclovir, valaciclovir, famciclovir) in pregnancy, no increase in major birth defects were reported in women exposed to either aciclovir or valaciclovir in the first trimester.^[9]

Efficacy of PEP in pregnant women

The efficacy of VZIG in preventing clinical chicken pox is known to be suboptimal and the results from studies are consistent. In a study of 212 seronegative women who

were given VZIG within 10 days of exposure 41% had clinical varicella infection.^[6] VZIG given within the first 3 days following exposure had the same efficacy (63 of 153 developed varicella). In an unpublished study from Kings College Hospital of 23 seronegative women who received VZIG <20 weeks, 8 developed clinical chickenpox; of the 7 more than 20 weeks who received VZIG, 5 developed clinical chickenpox. (overall 43%). Similarly, in a study of 20 years' experience in Italy, of 50 pregnant seronegative women follow up after receipt of VZIG as PEP, 21/50 (42%) developed clinical chickenpox.^[5]

In a Birmingham (UK) study, outcome information was obtained on 21 exposed women with IgG levels of <150mIU/ml who received VZIG. Of these 5 (24%) developed clinical chickenpox, similar to the proportion of women developing chickenpox in the absence of treatment (6/23; 26%).^[15]

There is little if any available data on the efficacy of aciclovir in preventing chicken pox in pregnant women, and no data on the efficacy of preventing congenital varicella infection. Theoretically aciclovir should be as least as effective at preventing severe varicella infection in the mother (greatest risk in later pregnancy) as in immunosuppressed patients where efficacy has been demonstrated. Prevention of transplacental infection of the foetus following with potential exposures in the first 20 weeks of pregnancy, using antivirals is less clear, not least as the optimal timing and duration of treatment are unknown.

Recommendation for Pregnant Contacts

In light of the existing evidence on the safety of aciclovir in the second and third trimesters of pregnancy, the efficacy of aciclovir in preventing clinical chickenpox in healthy and immunosuppressed contacts and the relative sub-optimal efficacy of VZIG as PEP in pregnant women, the following PEP is recommended.

All pregnant women who are exposed to chickenpox or shingles should be assessed for susceptibility as described in the national guidelines.^[1] If there is a previous history of chickenpox in the pregnant woman, she can be re-assured and no PEP is required. If there is no/unknown previous history of chickenpox in the pregnant woman, test for the presence of varicella antibodies in line with national guidelines.^[1]

- for susceptible women (quantitative assay <100mIU/ml) exposed in the first 20 weeks of pregnancy, VZIG is recommended
- for susceptible women (quantitative assay <100mIU/ml) exposed from 20 weeks of pregnancy, either VZIG or aciclovir (800mg 4 times a day from days 7 to 14 after exposure) is recommended for susceptible contacts. Oral valaciclovir 1000mg 3 times a day can be used as a suitable alternative

The day of exposure is defined as the date of the rash if the index is a household contact and date of first or only contact if the exposure is on multiple or single occasion(s) respectively. If the woman presents later than day 7 after exposure, a 7-day course of antivirals can be started up to day 14 after exposure, if necessary. If it has not been possible to perform the quantitative assay within the recommended time frame required for issuing VZIG, aciclovir can be given.

The decision on choice of PEP for women exposed from 20 weeks of pregnancy should take into account patient and health professional preference as well as the ability to offer and provide PEP in a timely manner.

Off label use of aciclovir and valaciclovir

As oral aciclovir and valaciclovir are not licensed for use in pregnancy, their use for women exposed after 20 weeks would be 'off label'. Clinicians are able to prescribe medicines outside the terms of the licence when it is in the best interest of the patient on the basis of available evidence. This evidence has been considered and recommended by the PHE convened expert working group (see Appendix 1 for membership).

Further advice on off-label prescribing is on the MHRA website:

www.gov.uk/drug-safety-update/off-label-or-unlicensed-use-of-medicines-prescribers-responsibilities#prescribing-in-a-patients-best-interests

When current practice supports the use of a medicine outside the terms of its licence, the MHRA advise that it may not be necessary to draw attention to this when seeking consent from patients. However, it is good practice to give as much information as patients or carers require or which they may see as relevant.

Contraindications and precautions to aciclovir and valaciclovir

In individuals with renal impairment or intestinal malabsorption, for example inflammatory bowel disease, VZIG may be considered. The dose of aciclovir may need to be adjusted in patients with renal impairment. See the British National Formulary (BNF) for more information.

Potential side effects of aciclovir and valaciclovir

The most commonly reported side effects from aciclovir can include dizziness, headache, nausea, vomiting, diarrhoea, abdominal pain, skin rashes, photosensitivity, pruritus, urticaria and fatigue. Further information about side effects on aciclovir and valaciclovir are available in the BNF.

Subsequent exposure to chickenpox or shingles during the same pregnancy

Women who have a second exposure during pregnancy, should be risk assessed and have a repeat VZV antibody test given the rates of seroconversion with both VZIG and aciclovir, in line with [national guidelines](#).^[1] Given the short half life of aciclovir/valaciclovir compared with VZIG, if there is a second exposure immediately after a course of antivirals, a second risk assessment and course should be given in the same way starting 7 days after the subsequent exposure.

Pregnant women presenting with chickenpox

If, despite having taken prophylactic aciclovir/valaciclovir, a pregnant woman presents with a chickenpox rash, they should be changed onto a therapeutic dose (aciclovir of 800mg 5 times a day or 1000mg valaciclovir 3 times a day for 7 days, starting from the day of onset of the rash). If severe chickenpox develops, the woman should be hospitalised and given IV aciclovir.

Refer to the [Viral Rash in Pregnancy](#)^[3] guidance for further details.

4. Neonates

There is no change in guidance for exposed neonates ^[2,1]

Duration of restrictions

PHE is keeping the situation under constant review. This guidance will remain in place until further notice.

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Appendix 1: Membership of expert working group

Chair: Professor Judy Breuer; Professor of Virology University College London, Honorary Consultant Virologist Great Ormond Street Hospital, Chair of the JCVI varicella subcommittee

Ruth Parry (secretariat): Immunisation and Countermeasures Division, PHE

Professor Liz Miller: Consultant Epidemiologist, Immunisation and Countermeasures Division, PHE

Professor Adam Finn: Professor of Paediatrics, Schools of Cellular and Molecular Medicine and of Population Health Sciences, University of Bristol

Professor Asma Khalil: Professor of Maternal Fetal Medicine, Fetal Medicine Unit, Department of Obstetrics and Gynaecology, St George's University of London, St. George's Hospital

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Professor Mary Ramsay: Head of Immunisation, Public Health England

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Dr. Kevin Brown: Consultant Medical Virologist, Immunisation and Countermeasures Division

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Dr. Jessica Bat., Consultant Paediatric Oncologist and Honorary Senior Clinical Lecturer, University Hospital Southampton

Sharon Webb: NHS Infectious Diseases in Pregnancy Programme Manager, PHE Screening

Alan Russell: Senior Principal Pharmacist and Associate Commercial Specialist, Vaccine & Medical Countermeasures, Commercial Directorate, Department of Health and Social Care