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# Updated restrictions on use of Varicella Zoster Immunoglobulin (VZIG) during supply shortage: advice to health professionals

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# Document information

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| **Title** | Updated restrictions on use of varicella zoster immunoglobulin (VZIG) during supply shortage |
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## Document history

| Date | Change made | Version number |
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| August 2018 | Changes to the guidance include:<br>• strengthening guidance on use of aciclovir in susceptible women with a significant exposure from weeks 20 of pregnancy from 'consider to 'recommend'<br>• use of valaciclovir as an alternative to aciclovir in women exposed from weeks 20 of pregnancy<br>• restriction of VZIG extended to include all immunosuppressed individuals, except for those where oral aciclovir /valaciclovir may be contraindicated | 2.0 |
| August 2018 | Clarification that if patients present after day 7 after exposure that a 7 day course of antivirals can be started up to day 14 after exposure. Corrected the references | 2.1 |

# Contents

# Executive summary

In response to a significant national shortage of varicella zoster immunoglobulin (VZIG) due to manufacturing issues, from 6th July 2018, the use of VZIG in pregnancy has been limited to susceptible pregnant women who have had a significant exposure to chickenpox or shingles in the first 20 weeks of pregnancy. As the majority of adults in England are immune to chickenpox, this change is likely to affect a very small proportion of the antenatal population.

On 1st August 2018, an urgent review was undertaken by an expert working group convened by Public Health England (PHE). Based on the current supply situation and evidence of efficacy and safety of antivirals for post exposure prophylaxis, these updated guidelines including further restrictions on the use of VZIG have been developed.

This group have advised that the restrictions on the use of VZIG in pregnancy should continue and strengthened the recommendation that susceptible pregnant women who have had a significant exposure after 20 weeks, should be given the oral anti-viral drug, aciclovir (800mg four times a day from day 7 to 14 after exposure). Valaciclovir can be considered as a suitable alternative.

In addition, the restrictions on the use of VZIG are being extended to immunosuppressed individuals. Susceptible individuals should now receive either aciclovir or valaciclovir in the event of a significant exposure, unless there is a specfic contraindication to these oral antiviral agents, when VZIG will still be required.

Guidance on the use of VZIG in neonates and susceptible women exposed in the first 20 weeks of pregnancy remain unchanged.

These restrictions will be kept under review in light of the ongoing supply situation.

# VZIG and its use

VZIG is a concentrated preparation of antibodies against chickenpox (varicella) derived from healthy non-UK blood donors. It is administered as a single intramuscular injection to exposed individuals at high risk of severe complications who are known to be susceptible to chickenpox. These groups are immunosuppressed individuals, neonates in the first week of life, and pregnant women.

PHE procure and issue VZIG on a named patient basis through over 70 issuing centres across England.

## Rationale for the changes in the use of VZIG

Historically, when supplies of VZIG have been limited, its use has been restricted in pregnant women to prioritise those groups likely to have the most severe impact from chickenpox. Since the last restrictions were in place in the early 1990s, there has been a growing body of evidence on the safety and efficacy of oral aciclovir as post exposure prophylaxis.

In light of the continuing significant shortage of VZIG, PHE urgently convened an expert working group on 1st August 2018, to review the implications of the supply shortage, to prioritise the use of the existing stock, and to advise on the management of exposures in high risk groups, focussing on the evidence of efficacy and safety of antivirals for post exposure prophylaxis.

## Current restrictions for VZIG

- **Pregnant women**

From 6th July 2018, VZIG is issued only to VZ antibody negative pregnant contacts exposed in the first 20 weeks of pregnancy i.e. up to and including 20+0 weeks.

For susceptible women exposed after 20 weeks i.e. from 20+1 weeks to delivery, oral aciclovir at 800mg four times a day from days 7 to 14 after exposure is recommended. Valaciclovir 1000mg three times a day from days 7 to 14 after exposure can be used as a suitable alternative.

- **Immunosuppressed individuals**

From 8th August 2018, VZIG will no longer be issued to susceptible immunosuppressed contacts following a significant exposure. Oral aciclovir or valaciclovir is recommended for these individuals, unless there are significant concerns of renal toxicity or malabsorption. For such individuals, VZIG will be issued following an appropriate risk assessment, including recommended antibody testing.

- **Neonates**

There are **no** changes to the guidance[1] for neonates.

In response to a significant national shortage of varicella zoster immunoglobulin (VZIG) due to manufacturing issues, from 6th July 2018, the use of VZIG in pregnancy has been limited to susceptible pregnant women who have had a significant exposure to chickenpox or shingles in the first 20 weeks of pregnancy. As the majority of adults in England are immune to chickenpox, this change is likely to affect a very small proportion of the antenatal population.

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In addition, the restrictions on use of VZIG are being extended to immunosuppressed individuals. Susceptible individuals should now receive either aciclovir or valaciclovir in the event of a significant exposure, unless there is a specfic contraindication to these oral antiviral agents, when VZIG will still be required.

Guidance on the use of VZIG in neonates and susceptible women exposed in the first 20 weeks of pregnancy remain unchanged.

These restrictions will be kept under review in light of the ongoing supply situation.

# 1. Pregnant women

## Why VZIG is given to pregnant women

Chickenpox infection during the first 20 weeks of pregnancy can lead to fetal varicella syndrome, which includes limb hypoplasia, microcephaly, cataracts, growth retardation and skin scarring. Chickenpox can cause severe maternal disease and this risk is greatest in the second or early in the third trimester.[2]

The rationale for the use of VZIG post exposure prophylaxis 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, VZIG 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 seven days of onset of maternal varicella.[2]

In recent years with sufficient VZIG supplies, VZIG has been recommended for VZ antibody negative pregnant contacts exposed to chickenpox at any stage of pregnancy providing it can be given within 10 days of contact with a case.[1]

## Efficacy of VZIG in pregnancy

About 50% of susceptible pregnant women given VZIG after a household exposure to chickenpox will develop clinical varicella, although the disease is usually attenuated and a further quarter will be infected sub-clinically.[2] Severe maternal varicella may still occur despite VZIG prophylaxis and prompt treatment with aciclovir is indicated in such cases.

## Recommended action for pregnant women not eligible for VZIG (>20+0 weeks)

Pregnant women in this group who are exposed to chickenpox or shingles should still 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
- 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 those identified as susceptible, oral aciclovir 800mg four

times a day from days 7 to 14 after exposure is recommended. Oral valaciclovir 1000mg three 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.

## Why aciclovir / valaciclovir is being recommended

Varicella infection (chickenpox) can cause severe maternal disease and this risk is greatest in the second or early in the third trimester. Although the majority of pregnant women are likely to be immune, susceptible pregnant women who are infected later in pregnancy may develop varicella pneumonia, hepatitis and encephalitis.

Historically, 10 to 14% of varicella cases in pregnancy were reported to have pneumonia, based on small case series [3]; in a more recent study of almost 1000 pregnant patients with chickenpox, the proportion with pneumonia was 2.5%, with no maternal deaths, probably reflecting improved medical care and use of aciclovir treatment.[4]

Occasional cases of fetal damage have been reported following maternal varicella between 20 and 28 weeks' gestation but the risk is substantially lower than in the first 20 weeks of pregnancy when typical fetal varicella syndrome occurs. Newborn babies whose mothers develop a chickenpox rash from 5 days before to 2 days after delivery are at risk of severe neonatal varicella, and historically fatalities occurred despite VZIG.

## Reason for starting antivirals at day 7 after exposure

In a study evaluating the comparative effectiveness of a 7 day 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. [5]

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

## Safety and efficacy of oral aciclovir / valaciclovir in pregnancy

The efficacy of oral aciclovir as post exposure prophylaxis has been demonstrated in healthy immunocompetent and immunosuppressed children. In a study of 13 immunocompetent children who were household contacts and treated 7-14 days after exposure, only one developed typical varicella illness. Two children developed a mild illness and the remaining ten seroconverted without any symptoms.[6] The recommended dose in pregnant women (800mg 4 times a day) is in line with the Royal College of Paediatrics and Child Health recommendations for prophylaxis in immunocompromised children.[7].

Although oral aciclovir and valaciclovir (prodrug of aciclovir) are not licensed in pregnancy, there is extensive evidence of safety in pregnancy, including from two large registries of infants whose mothers were exposed to aciclovir in pregnancy.[8;9] Aciclovir is also recommended for treatment of chickenpox in women who are more than 20 weeks pregnant.[3;10] 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.[8] In a Danish national cohort study of 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]

## 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 https://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 e.g. 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 and seek expert advice from the PHE Rabies and Immunoglobulin service.

## 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 five times a day or 1000mg valaciclovir three times a day for seven 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[11] guidance for further details.

# 2. Immunosuppressed individuals

## Why VZIG is given to immunosuppressed individuals

All immunosuppressed individuals as defined in Chapter 6 (Immunisation against infectious disease – the Green Book) [11] 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. VZIG is not indicated in immunosuppressed contacts with VZV IgG antibody ≥150mIU/ml as the amount of antibody provided by VZIG will not significantly increase VZV antibody levels.

Individuals receiving regular IVIG replacement therapy do not require VZIG if the most recent dose was administered ≤3 weeks before exposure.

All other immunosuppressed individuals who are not already on IVIG replacement therapy will require an assessment at the time of exposure. These individuals can be categorized into two groups [1]

- Group A includes most individuals with immunosuppression. These individuals should be able to develop and maintain adequate antibody from prior infection or vaccination.

- Group B includes individuals who are unlikely to have developed or maintained adequate antibody levels from prior infection or vaccination. Individuals in Group B may have lost immunity since their previous antibody tests due to procedures such as haematopoietic stem cell transplant or other immunosuppressive treatments

## Efficacy 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.[12] 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 two 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%.[13] 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. [14] This compares with a secondary infection rate of 18% in those not receving any post exposure prophylaxis (RR 8.5 (95%CI: 1.6-45.9)).

## Recommended action for exposed 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 [15] 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 bioavailabilty, 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 four times daily, days 7 to 14 after exposure | Not recommended |
| **Children 2-17 years of age** | 10mg/kg (up to a maximum of 800mg), four times daily days 7 to 14 after exposure | 20 mg/kg (up to a maximum 1000mg) three times daily, days 7 to 14 after exposure |
| **Adults** | 800mg four times daily, from days 7 to 14 after exposure | 1000mg three times daily, from days 7 to 14 after exposure |

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

## 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).[5]

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 https://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 e.g. 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 and seek expert advice from the PHE Rabies and Immunoglobulin service.

### 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. Neonates

There is no change in guidance for exposed neonates [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

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