28a

Shingles (herpes zoster)

The disease

Shingles (herpes zoster) is caused by the reactivation of a latent varicella zoster virus (VZV) infection, generally decades after the primary infection.

Primary VZV infection typically occurs during childhood and causes chickenpox (varicella); further information on this can be found in Chapter 34. Following primary VZV infection, the virus enters the sensory nerves and travels along the nerve to the sensory dorsal root ganglia and establishes a permanent latent infection. Reactivation of the latent virus leads to the clinical manifestations of shingles and is associated with immune senescence or suppression of the immune system i.e. immunosuppressive therapy, HIV infection, malignancy and/or increasing age. The annual incidence of shingles for those aged 70 to 79 years is estimated to be around 790 to 880 cases per 100,000 people in England and Wales (van Hoek *et al*., 2009), see Figure 1. The risk and severity of shingles increases with age.

The first signs of shingles begin most commonly with abnormal skin sensations and pain in the affected area of skin (dermatome). Headache, photophobia, malaise and less commonly fever may occur as part of the prodromal phase. Within days or weeks, a unilateral vesicular (fluid filled blisters) rash typically appears in a dermatomal distribution. In immunocompromised individuals, a rash involving multiple dermatomes may occur. The affected area may be intensely painful with associated paraesthesia (tingling, pricking, or numbness of the skin), and intense itching is common (Gilden *et al*., 1991). The rash typically lasts between two and four weeks.

Following the rash, persistent pain at the site, known as post herpetic neuralgia (PHN), can develop and is seen more frequently in older people. Pain that persists for, or appears more than, 90 days after the onset of rash (Oxman *et al*., 2005) is a commonly accepted definition for PHN. On average, PHN lasts from three to six months, but can persist for longer. The severity of pain can vary and may be constant, intermittent or triggered by stimulation of the affected area, such as by wind on the face. (Katz *et al*., 2004)

Other complications of shingles depend on the nerves affected and include paresis (motor weakness), facial palsy and 'herpes zoster ophthalmicus', with involvement of the eye and associated dermatome, which may result in keratitis, corneal ulceration, conjunctivitis, retinitis, optic neuritis and/or glaucoma. (Shaikh S *et al*., 2002; Pavan LD, 1995)

The reactivated virus can, in some cases, disseminate into the lungs, liver, gut, and brain, leading to pneumonia, hepatitis, encephalitis, and disseminated intravascular coagulopathy. Disseminated disease is more likely to occur in those who are severely immunocompromised, with a case fatality rate reported to be between 5 and 15%, and most deaths being attributable to pneumonia (Rogers *et al*., 1995; Gnann *et al*., 1991).

Individuals with active lesions, particularly if they are immunosuppressed, can transmit VZV to susceptible individuals to cause chickenpox and therefore at risk individuals who have had a significant exposure to shingles require post exposure management (see Chapter 34). There is no evidence that shingles can be acquired from another individual who has chickenpox.

History and epidemiology of the disease

Varicella infection is a prerequisite for the development of shingles. In temperate climates in the absence of a varicella vaccination programme, the lifetime risk for varicella infection is over 95% (Banz *et al*., 2003).

Although shingles can occur at any age, incidence increases with age (see Figure 1) with an estimated lifetime risk of one in four, (Miller *et al*., 1993). The increasing incidence with age is thought to be associated with age related immune senescence.

Age-specific incidence rates of shingles have been estimated using a number of different primary care derived data sources (van Hoek *et al*., 2009).

Data from GP-based studies in England and Wales suggest that over 50,000 cases of shingles occur in older people aged 70 years and over annually. The severity of shingles generally increases with age (Figure 1) and can lead to PHN that can require hospitalisation (Table 1). Studies have estimated ophthalmic zoster to occur in 10-20% of shingles cases (Opstelten *et al*., 2002) with around 4% of the cases resulting in long-term sequelae, including pain (Bowsher,1999).

It is estimated that, in people aged 70 years and over, around one in 1000 cases of shingles results in death (van Hoek *et al*., 2009), although due to the nature of the population and risk of co-morbidities some deaths recorded as being shingles related may not be directly attributable to the disease.

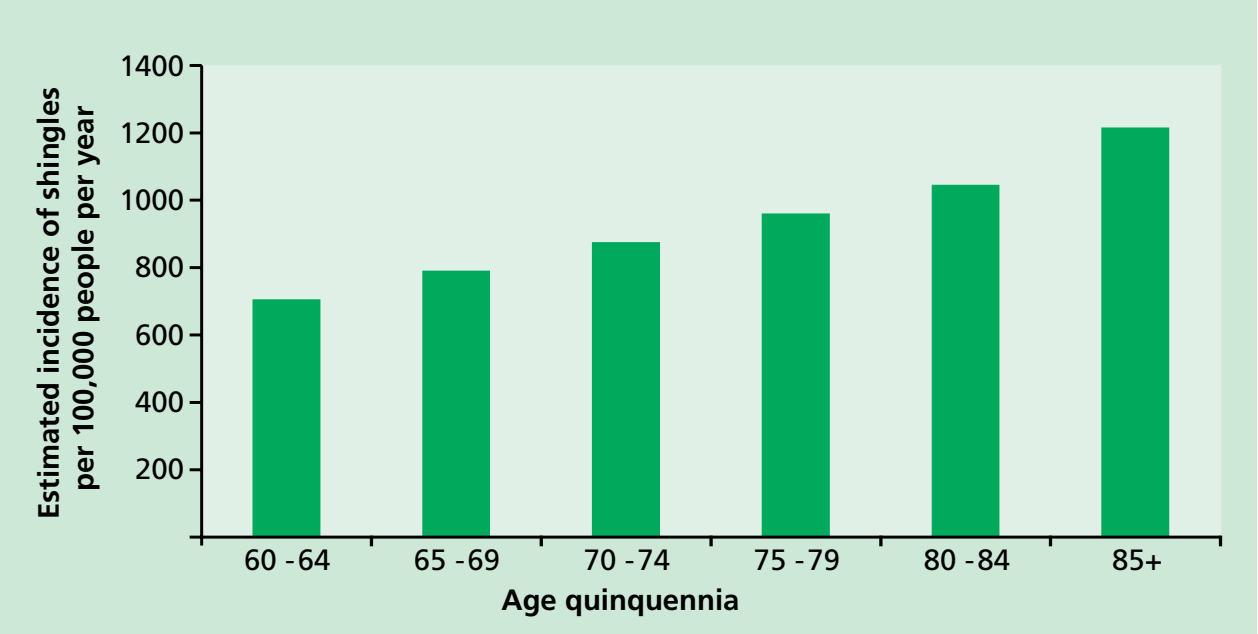

Figure 1 Estimated annual age-specific incidence of shingles per 100,000 per year in the immunocompetent population in England and Wales (population 2007). Data taken from van Hoek *et al.*, 2009.

Table 28a 1: Estimated percentage developing PHN by age group in the immunocompetent population in England and Wales (population 2007). Data taken from van Hoek *et al*., 2009.

	Age group					
	60-64 years	**65-69 years**	**70-74 years**	**75-79 years**	**80-84 years**	**85 years**
Proportion developing PHN after 90 days	9%	11%	15%	20%	27%	52%

The risk of shingles is also increased in individuals with certain conditions, including systemic lupus erythematosus, (Nagasawa *et al*.,1990) rheumatoid arthritis, (Smitten *et al*., 2007), diabetes (Heymann *et al* 2008) and Wegener's granulomatosis. (Wung *et al*., 2005).

A national shingles immunisation programme was introduced into the routine schedule for adults aged 70 years with a phased catch up programme for 71-79 years commencing in September 2013. At the time, the programme vaccinated eligible individuals using a single dose of Zostavax®, a live, attenuated virus derived from the Oka/Merck strain of varicella zoster virus, but at a significantly higher dose than the Varivax® varicella vaccine.

The choice of age group was based on evidence of cost effectiveness of Zostavax®. This age group were considered likely to have the greatest ability to benefit from vaccination (van Hoek *et al*., 2009) due to:

- the burden of shingles disease within this age group (which increases with age)
- the estimated effectiveness of Zostavax® within this age group (which decreases with age) and
- the duration of protection of Zostavax®

In the first real world assessment of vaccine effectiveness of the UK vaccine programme, effectiveness waned from 69% (95% CI 65-74%) in the first year after vaccination to 45% (95% CI 29-57%) by the third year. (Walker *et al* 2018)

In the first five years of the routine programme in England, an estimated 40,500 GP consultations and 1840 hospitalisations were averted through vaccination with Zostavax® (Andrews *et al*, 2020). These reductions were consistent with effectiveness in the routine cohorts (vaccinated aged 70) of between 37% (for hospitalised zoster) and 75% (for PHN consultations) and, in catch up cohorts (vaccinated aged 78 to 79) of between 49% (for hospitalised PHN) and 66% (for PHN consultations).

Coverage of the routine cohort (adults aged 70) has declined since the start of the programme from 61.8% in 2013/14 to 31.2% in 2021/22. Despite this, there is evidence of subsequent catch up as individuals remain eligible till their 80th birthday, with coverage reaching 80.7% for 79 year olds in 2021/2022.

In 2019 JCVI recommended Shingrix® should replace Zostavax® in the routine programme and that it should be offered routinely to adults aged 60 years (JCVI, 2019) based on cost effectiveness modelling. The risk of shingles and its complications increase with age and is high in individuals who are immunosuppressed. It is therefore important to ensure individuals are optimally protected at the time of greatest risk.

The shingles vaccination

From September 2023, Shingrix replaced Zostavax in the routine immunisation programme.

Shingrix® is a recombinant vaccine and contains varicella zoster virus glycoprotein E antigen produced by recombinant DNA technology, adjuvanted with $AS01_B$.

In the phase 3 randomized placebo controlled clinical trials of 15,411 participants, vaccine efficacy in the 7,695 immunocompetent adults ≥ 50 years and 6,950 ≥70 years, administered with two doses of Shingrix® 2 months apart was estimated at 97.2% and 91.2% respectively (Lal *et al* 2015),

In a phase 3 clinical trial in autologous haemopoietic stem cell transplant recipients aged 18 years and above who received two doses of Shingrix® 1-2 months apart, robust humoral and cellular responses persisted at 1 year after vaccination. (Dagnew *et al*, 2019) Post hoc efficacy analysis revealed a vaccine efficacy of 87.2% against herpes zoster in immunocompromised patients which included non-Hodgkin B-cell lymphoma and chronic lymphocytic leukaemia.

One and two dose real world vaccine effectiveness of Shingrix® was estimated at 56.9% and 70.1% respectively in a US study of adults aged >65 years (Izurieta *et al*, 2021). Two-dose vaccine effectiveness against postherpetic neuralgia was 76.0% (95% CI, 68.4-81.8). The two-dose vaccine effectiveness was not significantly lower for adults 80+ years, for second doses received at ≥180 days, or for individuals with autoimmune conditions.

Storage

The unreconstituted vaccines and diluent should be stored in the original packaging at +2°C to +8°C and protected from light. All vaccines are sensitive to some extent to heat and cold. Heat speeds up the decline in potency of most vaccines, thus reducing their shelf life. Freezing can also loss of potency for some vaccines. Effectiveness may be reduced unless the vaccine is stored at the correct temperature.

Presentation

Shingrix® is available as a white powder for reconstitution with diluent and is injected as a suspension. After reconstitution, the suspension is an opalescent colourless to pale brownish liquid.

Shingrix® is available in a pack size of 1 vial of powder plus 1 vial of suspension or in a pack size of 10 vials of powder plus 10 vials of suspension. The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or variation of appearance. If either is observed, the vaccine should not be administered.

After reconstitution, the vaccine should be used promptly; if this is not possible, the vaccine should be stored in a refrigerator (2°C – 8°C). If not used within 6 hours it should be discarded.

Dosage and schedule

Adults should receive two doses of **0.5ml** of Shingrix® a minimum of 8 weeks apart. However, a longer dose interval of between 6-12 months in England, Wales and Northern Ireland and 2-6 months in Scotland is being used.

Administration

Shingrix® should be given by intramuscular injection, preferably in the deltoid region of upper arm. Subcutaneous administration is not recommended. Shingrix® should be given with caution to individuals with thrombocytopenia or any coagulation disorder since bleeding may occur following intramuscular administration to these subjects. The vaccines must not be given intravascularly. Further information on injection technique can be found in Chapter 4.

Where Shingrix® vaccine is given at the same time as another vaccine, the vaccines should be given at separate sites, preferably in different limbs. If given in the same limb, they should be given at least 2.5cm apart (American Academy of Pediatrics, 2006).

The site at which each vaccine was given should be noted in the individual's records. See separate section on co-administration of Shingrix with other vaccines.

Disposal (also refer to Chapter 3)

Equipment used for vaccination, including used vials, ampoules, or partially discharged vaccines should be disposed of at the end of a session by sealing in a proper, puncture-resistant 'sharps' box according to local authority arrangements and guidance in the Health Technical Memorandum 07-01: Safe management of healthcare waste (NHS England, 2023).

Recommendations for the use of the vaccine

The aim of the national shingles immunisation programme is to lower the incidence and severity of shingles in older people.

From September 2023, Shingrix® (a recombinant sub-unit vaccine) which is given as a two-dose schedule, is the recommended vaccine for use in the routine programme.

National programme for adults aged 60-79 years

The JCVI recommended that Shingrix should replace Zostavax® in the routine programme and that the programme should be offered at 60 years of age. The choice of age group was based on evidence that the greatest number of cases would be prevented by administering the vaccine at this age. This is being rolled out over a period of years starting with those aged 65 and 70.

Those who have been previously eligible will remain eligible until their 80th birthday. Where an individual has turned 80 years of age following their first dose of Shingrix, a second dose should be provided before the individual's 81st birthday to complete the course.

The course consists of two doses of Shingrix®. For immunocompetent individuals the second dose may be offered eight weeks after the first dose. For operational reasons, a longer dose interval is being used (between 6-12 months in England, Wales and Northern Ireland and 2-6 months in Scotland). For severely immunosuppressed adults, these individuals need to be protected more quickly and therefore the second dose should ideally be given 8 weeks to 6 months after the first dose.

Adults aged 70 to 79 years prior to 1st September 2023 will be eligible for vaccination until their 80th birthday. Those previously eligible for Zostavax® will be offered Zostavax® whilst supplies remain. Zostavax® is given as a single dose course.

Shingrix® is not indicated for prevention of primary VZV infection (chickenpox) and should not be used in children and adolescents.

Severely immunosuppressed individuals aged 50 years and over

From September 2021, Shingrix® has been available to immunosuppressed individuals aged 70 to 79 years, who are contraindicated to receive Zostavax®, as part of the NHS shingles vaccination programme. The forthcoming change from 1 September 2023 will expand the eligibility to severely immunosuppressed individuals aged 50 years and over (with no upper age limit) who should be offered two doses of Shingrix. The second dose should be given 8 weeks to 6 months after the first dose for this cohort, in line with the Summary of Product Characteristics (SmPC).

Severely immunosuppressed individuals represent the highest priority for vaccination given their risk of severe disease, and therefore the programme aims to catch up all eligible individuals aged 50 years and over in the first year of programme implementation. Individuals who should be offered Shingrix® amongst this age group are summarized below (Box). If there is any doubt, individual patients should be discussed with their specialist.

Severely immunosuppressed individuals who have already received 2 doses of Shingrix® do not need re-vaccination.

Primary humoral immunodeficiencies such as X-linked agammaglobulinemia, are not of themselves an indication for earlier vaccination with Shingrix® unless associated with T cell defects. If there is any doubt, specialist advice from an immunologist should be sought.

Individuals who receive high dose short term immunosuppression at doses equivalent to ≤40mg prednisolone per day for acute episodes of illness such as asthma / chronic obstructive pulmonary disease (COPD) or COVID-19 are not considered severely immunosuppressed.

Shingrix® should not be offered earlier to those on replacement corticosteroids for adrenal insufficiency, or to those taking topical or inhaled corticosteroids or corticosteroid replacement therapy.

Box: Definition of severe immunosuppression for the Shingrix vaccine programme

Individuals with primary or acquired immunodeficiency states due to conditions including:

- acute and chronic leukaemias, and clinically aggressive lymphomas (including Hodgkin's lymphoma) who are less than 12 months since achieving cure
- individuals under follow up for chronic lymphoproliferative disorders including haematological malignancies such as indolent lymphoma, chronic lymphoid leukaemia, myeloma, Waldenstrom's macroglobulinemia and other plasma cell dyscrasias (N.B: this list not exhaustive)
- immunosuppression due to HIV/AIDS with a current CD4 count of below 200 cells/µl.
- primary or acquired cellular and combined immune deficiencies – those with lymphopaenia (<1,000 lymphocytes/ul) or with a functional lymphocyte disorder
- those who have received an allogeneic (cells from a donor) or an autologous (using their own cells) stem cell transplant in the previous 24 months
- those who have received a stem cell transplant more than 24 months ago but have ongoing immunosuppression or graft versus host disease (GVHD)

Individuals on immunosuppressive or immunomodulating therapy including:

- those who are receiving or have received in the past 6 months immunosuppressive chemotherapy or radiotherapy for any indication
- those who are receiving or have received in the previous 6 months immunosuppressive therapy for a solid organ transplant
- those who are receiving or have received in the previous 3 months targeted therapy for autoimmune disease, such as JAK inhibitors or biologic immune modulators including
- B-cell targeted therapies (including rituximab but for which a 6 month period should be considered immunosuppressive), monoclonal tumor necrosis factor inhibitors (TNFi), T-cell co-stimulation modulators, soluble TNF receptors, interleukin (IL)-6 receptor inhibitors.,
- IL-17 inhibitors, IL 12/23 inhibitors, IL 23 inhibitors (N.B: this list is not exhaustive)

Individuals with chronic immune mediated inflammatory disease who are receiving or have received immunosuppressive therapy

- moderate to high dose corticosteroids (equivalent ≥20mg prednisolone per day) for more than 10 days in the previous month
- long term moderate dose corticosteroids (equivalent to ≥10mg prednisolone per day for more than 4 weeks) in the previous 3 months
- any non-biological oral immune modulating drugs e.g. methotrexate >20mg per week (oral and subcutaneous), azathioprine >3.0mg/kg/day; 6-mercaptopurine >1.5mg/kg/day, mycophenolate >1g/day) in the previous 3 months
- certain combination therapies at individual doses lower than stated above, including those on ≥7.5mg prednisolone per day in combination with other immunosuppressants (other than hydroxychloroquine or sulfasalazine) and those receiving methotrexate (any dose) with leflunomide in the previous 3 months

Individuals who have received a short course of high dose steroids (equivalent >40mg prednisolone per day for more than a week) for any reason in the previous month.

Reinforcing immunisation

The need for booster doses following either 2 doses of Shingrix® or a single dose of Zostavax® has not yet been determined.

Co-administration with other vaccines

In line with general advice about co-administration of inactivated or non-live vaccines, Shingrix® can be given concomitantly with inactivated influenza vaccine. Initially, a seven-day interval was recommended between Shingrix® and adjuvanted influenza vaccine because the potential reactogenicity from two adjuvanted vaccines may reduce tolerability in those being vaccinated. Interim data from a US study on co-administration of Shingrix with adjuvanted seasonal influenza vaccine is reassuring. Therefore, an appointment for administration of the seasonal influenza vaccine can be an opportunity to also provide shingles vaccine, although the latter should be offered all year round, rather than purely as a seasonal programme.

Shingrix® can also be given concomitantly with the 23-valent pneumococcal polysaccharide vaccine (PPV23). In phase III controlled open label clinical studies of Shingrix® in adults aged 50 years and older, individuals received PPV-23 with their first dose of Shingrix®. The immune responses of the co-administered vaccines were unaffected, although fever and shivering were more commonly reported when PPV-23 was given with Shingrix®.

As Shingrix® is a non-live vaccine, where individuals in an eligible cohort present having recently received another inactivated or live vaccine, Shingrix® vaccination should still be offered. In such circumstances, patients should be informed about the likely timing of potential adverse events relating to each vaccine.

Previous incomplete vaccination

If the course of Shingrix® is interrupted or delayed, it should be resumed as soon as possible but the first dose should not be repeated.

Pregnancy

There is no known risk associated with giving inactivated, recombinant viral or bacterial vaccines or toxoids during pregnancy or whilst breast-feeding (Kroger *et al*., 2013). If indicated, Shingrix® can be considered in pregnancy after full discussion of the risks and benefits of vaccination with the recipient.

Contraindications

Shingrix®

Shingrix® should not be administered to an individual with a history of a confirmed anaphylactic reaction to any component of the vaccine.

Severe Immunosuppression

Individuals aged 50 years and above with severe immunosuppression (see box page 7) should be offered Shingrix® vaccination. Individuals with lower levels of immunosuppression should be offered Shingrix® vaccination if they are within an eligible age cohort for the routine programme.

Individuals aged 50 years and older anticipating immunosuppressive therapy

The risk and severity of shingles is considerably higher amongst severely immunosuppressed individuals and therefore eligible individuals anticipating immunosuppressive therapy should ideally be assessed for vaccine eligibility before starting treatment. Eligible individuals who have not previously been vaccinated should commence a course of Shingrix® at the earliest opportunity and at least 14 days before starting immunosuppressive therapy with a dose interval of 8 weeks, although leaving one month would be preferable. If immunosuppressive treatment is subsequently commenced after the first dose of Shingrix is given, the second dose may be given 8 weeks to 6 months later.

Individuals aged 18 – 49 years receiving stem cell transplant

Individuals who have received a stem cell transplant are at a particularly increased risk of developing herpes zoster which may have severe and debilitating effects. This risk is elevated regardless of patient age. Studies have shown that within immunosuppressed populations, stem cell transplant patients are at the highest risk of herpes zoster (McKay *et al*.).

In recognition of this, it is reasonable to give adult stem cell transplant recipients who are not otherwise eligible two doses of Shingrix® vaccine as part of their overall treatment plan. This includes adult recipients of allogenic transplant, autologous transplant or a CAR-T (chimeric antigen receptor T-Cell) therapy. The second dose of Shingrix® should be given 8 weeks – 6 months after the first dose.

Management of at risk individuals following significant exposure to herpes zoster

Transmission of VZV can occur following direct contact with herpes zoster lesions, resulting in chickenpox in contacts who are susceptible to VZV. Therefore, individuals at high risk of severe complications from varicella infection should be assessed for the need for post exposure management with antivirals (see Chapter 34 or Guidelines on post exposure prophylaxis for chickenpox and shingles (UKHSA, 2023) for further details).

Shingrix® is not recommended for use as post-exposure prophylaxis or as a treatment for chickenpox or shingles.

Precautions

Immunisation of individuals who are acutely unwell should be postponed until they have recovered fully. This is to avoid confusing the diagnosis of any acute illness by wrongly attributing any sign or symptoms to the adverse effects of the vaccine.

Shingrix® vaccination is not recommended for the treatment of shingles or post herpetic neuralgia (PHN). Individuals who have shingles should wait until symptoms have ceased before being considered for shingles immunisation. The natural boosting that occurs following an episode of shingles, however, makes the benefit of offering zoster vaccine immediately following recovery unclear. Patients who have two or more episodes of shingles in one year should have immunological investigation prior to vaccination. Clinicians may wish to discuss such cases with local specialist teams.

Concurrent administration of Shingrix® and anti-viral medications known to be effective against VZV has not been evaluated, but drugs such as aciclovir are unlikely to reduce vaccine response as the vaccine is a recombinant vaccine.

Transmission after vaccination

As Shingrix® is a recombinant protein vaccine there are no risks of developing varicella-like rashes following administration of Shingrix®.

Testing of post vaccination rashes

Although Zostavax® is no longer in routine use, in the event of a person developing a varicella (widespread) or shingles-like (dermatomal) rash at any time post-Zostavax® or Shingrix a vesicle fluid sample should also be sent for analysis to confirm the diagnosis and determine whether the rash is vaccine associated or wild type. This service is available at the Virus Reference Department (VRD) at the UK Health Security Agency (UKHSA), Colindale (T: 0208 327 6017). Please note sampling kits are not supplied by the Virus Reference Department at UKHSA. Health professionals are requested to obtain vesicle swabs from their local hospital laboratories. Forms and instructions on how to take a vesicle fluid sample can be found at: https://www.gov.uk/government/publications/varicella-zoster-virus-referral-form

Inadvertent vaccination in individuals under 18 years of age

Shingrix® is licensed for use in individuals over 18 years of age. However, most children above the age of 10 are likely to be immune to varicella and therefore inadvertent vaccination with Shingrix® is highly unlikely to result in serious adverse reactions. As the vaccine is a recombinant sub-unit vaccine inadvertent vaccination with Shingrix® in varicella naïve children of any age is unlikely to result in serious adverse reactions and would count as a valid dose of varicella vaccine. In this instance, children eligible for chickenpox vaccination may be offered a second dose, a minimum of 4 weeks later, to complete the course

Inadvertent vaccination with Shingrix® during pregnancy

There is no known risk associated with giving inactivated, recombinant viral or bacterial vaccines or toxoids during pregnancy or whilst breast-feeding (Kroger *et al.*, 2013). If indicated, Shingrix® can be considered in pregnancy after full discussion of the risks and benefits of vaccination with the recipient.

All incidents of inadvertent administration of Shingrix ® during pregnancy should also be reported to UK Health Security Agency (UKHSA) using the vaccine administered in pregnancy reporting form (ViP). https://www.gov.uk/vaccination-in-pregnancy-vip

Adverse reactions

The safety of Shingrix® has been evaluated in clinical trials; in those aged 50 years and above the most frequently reported side effects were pain at the injection site (68%), myalgia (33%), and fatigue (32%). Most of these reactions were not long-lasting (median duration 2-3 days).

A full list of side effects can be found in the Shingrix® summary of product characteristics. (https://www.medicines.org.uk/emc/product/12054/smpc)

Serious suspected adverse reactions to Shingrix® should be reported to the Medical and Healthcare products Regulatory Agency (MHRA) using the Yellow Card reporting scheme (www.mhra.gov.uk/yellowcard).

Supplies

Shingrix® is manufactured by GlaxoSmithKline ; the marketing authorization holder is GlaxoSmithKline UK Limited (Tel: 0800 221 441).

In England, these vaccines should be ordered online via the ImmForm website (www.immform.dh.gov.uk) and it is distributed by Movianto UK (Tel: 01234 248631) as part of the national immunisation programme. Further information about ImmForm is available at https://portal.immform.phe.gov.uk/ or from the ImmForm helpdesk at helpdesk@immform.org.uk or Tel: 0844 376 0040

Centrally purchased vaccines for the national immunisation programme for the NHS can only be ordered via ImmForm and are provided free of charge to NHS organisations.

Vaccines for private prescriptions, outbreaks, occupational health use or travel are NOT provided free of charge and should be ordered from the manufacturers.

To obtain supplies of Shingrix® for use outside of the national immunisation programme contact GlaxoSmithKline UK, direct on Tel: 0800 221 441.

In Scotland, supplies should be obtained from local vaccine-holding centres. Details of these are available from National Procurement (Tel. 0131 275 7587)

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