Infanrix Hexa or Vaxelis

Newborn use only

2023

Alert	**Infanrix Hexa**: Ensure the pre-filled syringe containing the diphtheria, tetanus and pertussis toxoid is mixed with the vial containing the HIB component of the vaccine. Consent from parent/guardian is to be obtained prior administration. Preterm infants should receive vaccines according to the recommended schedule at their chronological age, without correction for prematurity, provided they are medically stable and there are no contraindications to vaccination.(1) A primary series should be given using the same hexavalent vaccine. If this is not possible, providers may use the alternative hexavalent vaccine brand to complete the series. Providers will receive either Vaxelis® or Infanrix® Hexa, with the option to place a special order for the alternate hexavalent vaccine for children who have commenced their primary course with that vaccine brand. (16)
Indication	1. Primary immunisation against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type B at 6 weeks/2 months, 4 and 6 months from the date of birth. (1,2) 2. Catch-up vaccination schedules in children < 10 years of age.
Action	Induces the production of antibodies against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type B infection.
Drug type	Combination vaccine - DTPa-hepB-IPV-Hib — diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus-Haemophilus influenzae type b combination vaccine.
Trade name	Infanrix Hexa, Vaxelis
Presentation	Infanrix-Hexa suspension for injection: comes as a combination pack of (1) a prefilled syringe with a suspension (containing, diphtheria toxoid, tetanus toxoid, acellular pertussis vaccine, inactivated polioviruses, hepatitis B surface Ag) and (2) vial containing pellet Haemophilus influenzae type B capsular polysaccharide. (1,6) Vaxelis suspension for injection: comes as single suspension of the 6 vaccine components (diphtheria toxoid, tetanus toxoid, acellular pertussis vaccine, inactivated polioviruses, hepatitis B surface Ag, and Haemophilus influenzae B capsular polysaccharide (1,7)
Dose	0.5 mL at 2 months (6 weeks), 4 and 6 months of life.* *Same schedule for both preterm and term infants.
Dose adjustment	Not applicable
Maximum dose	Not applicable
Total cumulative dose	Not applicable
Route	IM
Preparation	See below
Administration	1. May administer oral sucrose or EBM 2 minutes prior to injection (observe local pain policy). 2. Preparation **<u>Infanrix-Hexa</u>** 1.Gently shake the pre-filled syringe. 2. Add its contents to the vial of Hib pellet and shake until pellet is completely dissolved. **<u>Vaxelis</u>** Ready to use syringe. 3. Administer 0.5 mL of reconstituted suspension by intramuscular injection (IMI) to the anterolateral aspect of the thigh (slowly to reduce pain). 4. Administer on the opposite limb from other concurrently administered vaccines (e.g. Prevenar 13).
Monitoring	Observe for 15 minutes after vaccination for any Adverse Event Following Immunisation (AEFI). Pain: Refer to local pain relief policy. Apnoea and bradycardia in premature infants for up to 48 hours after the first dose.(8-15) Infants with a history of febrile convulsions should be closely followed up as such adverse events may occur within 48-72 hours post-vaccination. (1)
Contraindications	Anaphylaxis following a previous dose of any DTPa vaccine. Hypersensitivity to any vaccine component.
Precautions	Significant acute illness or temperature greater than 38.5°C – postpone vaccine until neonatologist approves. Encephalopathy of unknown aetiology occurring within 7 days after previous vaccination with a pertussis containing vaccine. The following reactions to a previous dose may preclude further doses: - Convulsions within 72 hours.

	- Persistent, severe, inconsolable crying for three or more hours within 48 hours. - Unexplained temperature > 40.5°C within 48 hours. Immunosuppressed patients Thrombocytopaenia or bleeding disorders. Children who have had a Serious adverse events following immunisation (AEFIs)should receive further doses under close medical supervision. State and territory public health authorities- external site can provide information about specialist immunisation clinics, or the contact details for paediatricians or medical specialists with experience in managing people who have had an AEF.
Drug interactions	Tetanus Immune Globulin or Diphtheria Antitoxin, if used, should be given at a separate site, with a separate needle and syringe. Should not be given to infants or children on anticoagulant therapy unless the potential benefit clearly outweighs the risk of administration. Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines.
Adverse reactions	Common: Pain, inflammation, redness, injection site mass persisting for up to a few days. Uncommon: Headache, fever, lethargy, malaise, myalgia. Rare: Anaphylaxis, urticaria and peripheral neuropathy. Any serious or unexpected adverse event following immunisation should be reported promptly. Providers should use clinical judgment in deciding which adverse events to report and parents/carers should be encouraged to notify the immunisation service provider or health authorities of any untoward medical occurrence that follows immunisation. Each State/Territory has its own contact details for notification. Contact telephone number for NSW Public Health Unit is 1300 066 055.
Compatibility	Not applicable
Incompatibility	Do not mix with any other vaccines in the same syringe.
Stability	Infanrix-Hexa: After reconstitution, vaccine should be injected promptly. However, the vaccine is stable for up to eight hours at room temperature.
Storage	Store in a dedicated monitored vaccination fridge between +2 and +8°C. Do NOT freeze. Discard if the vaccine has been frozen. Protect from light.
Excipients	Infanrix-Hexa: Lactose, medium 199 (as stabiliser containing amino acids, mineral salts, vitamins and other substances), sodium chloride, aluminium hydroxide, aluminium phosphate and water for injections. The vaccine also contains the following residues: potassium chloride, polysorbate 20 and 80, formaldehyde, glycine, dibasic sodium phosphate dihydrate, monobasic potassium phosphate, neomycin sulfate and polymyxin B sulfate. (7) Vaxelis: Aluminum phosphate, Aluminum hydroxyphosphate sulfate. May also contain traces of glutaraldehyde, formaldehyde, neomycin, streptomycin, polymyxin B, bovine serum albumin.(7)
Special comments	AS of August 2023, Vaxelis is provisionally registered with Therapeutic Goods Australia and therefore is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.
Evidence	**Efficacy** Infanrix Hexa was highly immunogenic for the vaccine antigens diphtheria and tetanus toxoids, poliovirus type 1, 2 and 3 antigens, pertussis antigens (PT, FHA and PRN), HBsAg and the Hib antigen (polyribosylribitol phosphate [PRP]) both as primary and booster vaccination in healthy infants aged < 2 years, with antibodies against these antigens persisting in the long term.(3) Seroprotective titres against these antigens were achieved in 95–100% of Infanrix Hexa recipients. (3) Well-established serological correlates of protection exist for antibodies against tetanus, diphtheria, hepatitis B, polio and Hib. (4) Infanrix Hexa was administered concomitantly with a rotavirus vaccine (Rotarix) in a randomised, double-blind, placebo-controlled trial and with a 13-valent-pneumococcal vaccine (Prevenar-13) in several studies. Limited data from these studies suggest that co-administration of these vaccines with Infanrix Hexa does not affect the immunogenicity of either co-administered vaccine. (3)

Infanrix Hexa can be co-administered with other live or inactivated vaccines without interference with the immune response. (4)

Safety

Available clinical data from more than 10 years' experience with the vaccine suggest that Infanrix Hexa as primary and booster vaccination is a safe and useful option for providing protection against the common childhood diseases of diphtheria, tetanus, poliomyelitis, pertussis, hepatitis B and invasive Hib disease. (1,3)

A course of injections with Infanrix Hexa was as effective at producing protective levels of antibodies as giving separate vaccines containing the same active substances. Overall, between 95 and 100% of the children had antibodies to diphtheria, tetanus, pertussis, hepatitis B virus, polioviruses, and Hib, 1 month after the vaccination course.(5)

In 2007 the Committee for Medicinal Products for Human Use reviewed cases of apnoea in preterm infants following vaccination and concluded that the apnoea occurred due to immaturity of the immune system. Hence, their recommendation is to monitor very preterm infants for up to 48–72 hours after vaccination. (4)

Historical concerns about potential temporal association between sudden unexpected death (SUD) and hexavalent vaccines has been extensively investigated and in 2003 the European Medicines Agency concluded absence of a cause-effect relationship and no change in the benefit-risk profile of then available hexavalent vaccines. (4)

Safety in preterm infants <37 weeks: A 2019 systematic review in preterm infants <37 weeks includes 37 articles on preterm vaccination published in 2008-2018 in PubMed. Both live attenuated and inactivated vaccines are safe and well tolerated in preterm infants. Local reactions, apnea and reactivity changes are the most frequently reported adverse events. Lower gestational age and birth weight, preimmunization apnea, longer use of continuous positive airway pressure (CPAP) were risk factor for apnea.(8) The review recommended that neither gestational age nor birth weight should delay the decision to start vaccination in clinically stable preterm infants. Postponing vaccination is justified only in clinically unstable infants. If preterm infants are still hospitalized at the time at which they should be vaccinated they should receive their first vaccine in the neonatal ward monitoring them for 48–72 h after vaccination. This is particularly important for infants born ≤31 weeks GA, with birth weight <2 Kg, with pre-vaccination apnea episodes or with severe bronchopulmonary dysplasia.(8) The limitation of this systematic review was the data about extreme preterm infants are poor and a distinction of results according to grade of prematurity was not always performed in the studies enrolled.

Safety in the hospitalised preterm infants <32 weeks: Wilinska et al. studied 138 infants born before 37 weeks of gestation (73 born ≤28 weeks GA and 65 born >28 weeks GA), who underwent vaccination as inpatient and monitored their cardiac and respiratory functions as well as body temperature over 72 hours after DTaP-IPV-PCV-Hib vaccination. Apnea and changes in reactivity (i.e. change in infants' behaviour) were the relatively most frequent reported AEs. Infants who experienced apneas had significantly more frequently late onset sepsis and a history of longer use of continuous positive airway pressure (CPAP).(9) In the study by Anderson et al. the incidence of apnea after the first DTaP-IPV- PCV-Hib vaccination was 8.4% in extremely preterm infants, while there was no reaction following the second dose at 4 months. Infants with apnea following the 2-month vaccine displayed significantly lower GA and birth weight. (10) In a prospective study by Furck et al. the risk of apnea decreased with increasing GA [57]. In this study the frequency of apnea/bradycardia after the first dose of DTaP-IPV-PCV-Hib vaccine in 473 preterm infants with a weight <1500 g was 10.8%. (11) In a retrospective observational study by Flatz-Jequier et al. including 64 very low birth weight PIs aged <32 weeks, 33 infants developed a cardiorespiratory event after the first dose of DTaP-IPV-Hib vaccination and 6 of them required medical interventions after the second vaccine for a similar event, identifying a positive history of previous analogous AE as a significant risk factor for the recurrence of a cardiorespiratory event. (12). In the study by Clifford et al. evaluating the frequency of apnea and bradycardia up to 48 hours after DTPa-IPV-HBV-Hib-PCV7 and oral rotavirus vaccine at 2 and 4 months of age, 7 out of 38 preterm infants developed recurrent apnea after vaccination. Lower birth weight and ongoing hospitalization for complications related to prematurity increased the risk of a recurrent apnea following vaccination (13). A multi-centre retrospective cohort study by De Meo et al. including 13926 extremely preterm infants showed an increase in the respiratory support need in the 3 days following vaccination compared with the 3 days preceding the procedure, particularly in infants of 23-34 weeks of GA compared with older preterm infants (14). A retrospective, single-centre, observational study in infants <32 weeks gestation at Thomas Jefferson University Hospital evaluated the number of cardiorespiratory events (apnea, bradycardia, and desaturations) in the 72 hours before and after 2-month vaccination. The results suggest a link between

	immunization and increased risk of desaturation and bradycardia but did not provide significant evidence to support a link with increased risk of apnea. This indicates that neonates who experience frequent cardiorespiratory events should be closely monitored. (15)
Practice points	1. Do not give Infanrix Hexa or Vaxelis at birth. 2. Preterm infants should be vaccinated according to their chronological age from birth. 3. Immune response to some Hib conjugate vaccines has been reduced in infants born prematurely. 4. The first dose of Infanrix Hexa or Vaxelis can be given at 6 weeks of age due to the high morbidity and occasional mortality associated with pertussis in very young infants. If the first dose is given at 6 weeks of age, the next scheduled doses should still be at 4 and 6 months. 5. Paracetamol may be prescribed (15 mg/kg/dose) for administration at 4 hourly intervals after immunisation (maximum of 4 doses in a 24 hour period) for a fever > 38.5°C or significant pain if the child is miserable. Prophylactic administration of paracetamol at the time of, or immediately after, vaccination to reduce the risk of fever is not routinely recommended, with the exception of children < 2 years of age receiving meningococcal B vaccine and whole cell pertussis (DTPa). 6. The vastus lateralis muscle in the anterolateral thigh is the recommended site for IM vaccination in infants < 12 months of age. The deltoid muscle or ventrogluteal area is the recommended site for IM vaccination in children > 12 months of age. 7. Children with congenital limb malformation(s) should receive their vaccines in an unaffected limb where possible. The ventrogluteal area can also be considered. 8. NSW Health provides free antenatal pertussis vaccinations for every woman during every pregnancy. 9. There is currently no evidence to suggest infants require an extra DTPa vaccine at 18 months of age if their mother received antenatal pertussis vaccine. 10. Interruption of the recommended schedule with a delay between doses should not interfere with the final immunity achieved with Infanrix Hexa. Refer to The Australian Immunisation Handbook (1) for catch-up schedule.
References	1. Australian Immunisation Handbook. Infanrix Hexa and Vaxelis. Accessed on 21 August 2023. 2. National Immunisation Schedule. Accessed on 21 August 2023. 3. Dhillon S. DTPa-HBV-IPV/Hib Vaccine (Infanrix Hexa): A Review of its Use as Primary and Booster Vaccination. Drugs 2010; 70(8): 1021-58. 4. Baldo V, Bonnani P, Castro M & et al. Combined hexavalent diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus-Haemophilus influenzae type b vaccine – Infanrix Hexa. Human Vaccines & Immunotherapeutics 2014; 10 (1): 129-137. 5. European Medicines Agency. Infanrix hexa: summary of product characteristics [online]. 6. Infanrix-Hexa. Product Information. Accessed via MIMS online on 21 August 2023. 7. Vaxelis. Product Information. Accessed via MIMS online on 21 August 2023. 8. Elena Chiappini, Chiara Petrolini, Elena Sandini, Ameila Licari, Lorenza Pugni, Fabio A Mosca & Gianluigi Marseglia (2019): Update on vaccination of preterm infants: a systematic review about safety and efficacy/effectiveness. Proposal for a position statement by Italian Society of Pediatric Allergology and Immunology jointly with the Italian Society of Neonatology., Expert Review of Vaccines, DOI: 10.1080/14760584.2019.1604230. 9. Wilińska M, Warakomska M, Głuszczak-Idziakowska E, Jackowska T. Risk factors for adverse events after vaccinations performed during the initial hospitalization of infants born prematurely. Developmental period medicine. 2016 Jan 1;20(4):296-305. 10. Anderson J, Noori K, Morris SA. Apnoea after the 2-month immunisation in extremely preterm infants: What happens with the 4-month immunisation?. Journal of paediatrics and child health. 2013 Mar;49(3):E217-20. 11. Furck AK, Richter JW and Kattner E. Very low birth weight infants have only few adverse events after timely immunization. Journal of Perinatology.2010; 30:118–21 12. Flatz-Jequier A, Posfay-Barbe KM, Pfister RE, Siegrist CA. Recurrence of cardiorespiratory events following repeat DTaP-based combined immunization in very low birth weight premature infants. J Pediatr.2008;153:429–31. 13. Clifford V, Crawford NW, Royle J, Lazzaro T, Danchin M, et al. Recurrent apnoea post immunisation: informing re-immunisation policy. Vaccine.2011;29:7–5681. 14. DeMeo SD, Raman SR, Hornik CP, Wilson C, Clark R et al. Adverse Events After Routine Immunization of Extremely Low Birth Weight Infants. JAMA Pediatr.2015; 169: 740–45. 15. Tonnessen, Julia and Urday, MD, Pedro, "Assessing the Temporality of Adverse Effects of Vaccines in the NICU" (2020).Phase 1.Paper 2. https://jdc.jefferson.edu/si_hs_2022_phase1/2.

	16. NSW Health Letter to General Practitioners and Aboriginal Medical Services. Immunisation Schedule changes 1 July 2023. Introduction of New Hexavalent Vaccine 'Vaxelis.

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