For the use only of Registered Medical Practitioners or a Hospital or a Laboratory

VARILRIX

1. GENERIC NAME

Varicella Vaccine, Live IP.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.5 ml of the reconstituted vaccine contains:
Live attenuated varicella virus (OKA strain, propagated in MRC5 human diploid cells)….
not less than $10^{3.3}$ plaque-forming units (PFU)

List of excipients:

Powder: Anhydrous Lactose, Sorbitol, Mannitol, Amino acids.

Solvent: Water for injections.

This vaccine contains a trace amount of neomycin. see section *4.3 Contraindications*.
Neomycin sulphate is present as a residual from the manufacturing process.

Excipients with known effect:
The vaccine contains 6 mg of sorbitol per dose.
The vaccine contains 331 micrograms of phenylalanine per dose (see section 4.4).

3. DOSAGE FORM AND STRENGTH

Powder and solvent for solution for injection in pre-filled syringe.
Before reconstitution, the powder is slightly cream to yellowish or pinkish coloured cake and the solvent is a clear colourless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VARILRIX is indicated for active immunisation against varicella of healthy subjects and susceptible healthy close contacts from the age of 12 months onwards.

Susceptible healthy close contacts should be immunised in order to reduce the risk of transmission of virus to high-risk patients. These include parents and siblings of high-risk

patients, and medical, paramedical personnel and other people who are in close contact with varicella patients or high-risk patients.

4.2 Posology and method of administration

Posology

The immunisation schedules for *VARILRIX* should be based on official recommendations.

Healthy individuals

Children from 12 months of age, adolescents and adults
Children from the age of 12 months as well as adolescents and adults receive two doses of *VARILRIX* to ensure optimal protection against varicella (see section 5.1). The second dose should generally be given at least 6 weeks after the first dose. Under no circumstances should the interval between the doses be less than 4 weeks.

Individuals at high risk of severe varicella
Individuals at high risk of severe varicella may benefit from re-vaccination following the 2-dose schedule (see section 5.1). Periodic measurement of varicella antibodies after immunisation may be indicated in order to identify those who may benefit from re-immunisation. Under no circumstances should the interval between the doses be less than 4 weeks.

Interchangeability

A single dose of *VARILRIX* may be administered to subjects who have already received a single dose of another varicella-containing vaccine.

A single dose of *VARILRIX* may be administered followed by a single dose of another varicella-containing vaccine.

Method of administration

VARILRIX is to be injected subcutaneously (SC) in the deltoid region or in the anterolateral area of the thigh.

For instructions on reconstitution of the medicinal product before administration, see section *8.4 Storage and Handling Instructions*.

4.3 Contraindications

VARILRIX is contraindicated in individuals with severe humoral or cellular (primary or acquired) immunodeficiency such as (see also section *4.4 Special warnings and precautions for use.):*

- subjects with immunodeficiency states with a total lymphocyte count less than 1,200 per mm^3;
- subjects presenting other evidence of lack of cellular immune competence (e.g. patients with leukaemias, lymphomas, blood dyscrasias, clinically manifest HIV infection);
- subjects receiving immunosuppressive therapy including high dose of corticosteroids;
- severe combined immunodeficiency;
- agammaglobulinemia;
- AIDS or symptomatic HIV infection or an age-specific CD4+ T-lymphocyte percentage in children below 12 months: CD4+ <25%; children between 12-35 months: CD4+ < 20%; children between 36-59 months: CD4+ < 15%.

Hypersensitivity to the active substance or to any of the excipients listed in section 2 or to neomycin. However, a history of contact dermatitis to neomycin is not a contraindication.

VARILRIX is contraindicated in subjects having shown signs of hypersensitivity after previous administration of varicella vaccine.

Pregnancy- Furthermore, pregnancy should be avoided for 1 month following vaccination (see section *4.6 Use in Special Populations*).

4.4 Special warnings and precautions for use

As with other vaccines, the administration of *VARILRIX* should be postponed in subjects suffering from acute severe febrile illness. However, the presence of a minor infection, such as a cold, should not result in the deferral of vaccination.

Syncope (fainting) can occur following, or even before any vaccination especially in adolescents as a psychogenic response to the needle injection . This can be accompanied by several neurological signs such as transient visual disturbances, paraesthesia and tonic-clonic movements during recovery. It is important that procedures are in place to avoid injury from faints.

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic reaction following the administration of the vaccine.

Alcohol and other disinfecting agents must be allowed to evaporate from the skin before injection of the vaccine since they can inactivate the attenuated viruses in the vaccine.

Limited protection against varicella may be obtained by vaccination up to 72 hours after exposure to natural disease (see section *5.2 Pharmacodynamic properties*).

As with any vaccine, a protective immune response may not be elicited in all vaccinees.

As for other varicella vaccines, cases of varicella disease have been shown to occur in persons who have previously received *VARILRIX*. These breakthrough cases are usually mild, with a fewer number of lesions and less fever as compared to cases in unvaccinated individuals.

Transmission
Transmission of the Oka varicella vaccine virus has been shown to occur at a very low rate in seronegative contacts of vaccinees with rash. Transmission of the Oka varicella vaccine virus from a vaccinee who does not develop a rash to seronegative contacts cannot be excluded.
Compared to healthy vaccinees, leukaemia patients are more likely to develop a papulovesicular rash (see also *section 4.8 Undesirable effects*). In these cases too, the course of the disease in the contacts was mild.
Vaccine recipients, even those who do not develop a varicella-like rash, should attempt to avoid contact, whenever possible, with high-risk individuals susceptible to varicella for up to 6 weeks following vaccination. In circumstances where contact with high-risk individuals susceptible to varicella is unavoidable, the potential risk of transmission of the varicella vaccine virus should be weighed against the risk of acquiring and transmitting wild-type varicella virus.
High-risk individuals susceptible to varicella include:

- Immunocompromised individuals (see *sections 4.3 Contraindications* and *4.4 Special warnings and precautions for use*);
- Pregnant women without documented positive history of varicella (chickenpox) or laboratory evidence of prior infection;
- Newborns of mothers without documented positive history of chickenpox or laboratory evidence of prior infection.

The mild nature of the rash in the healthy contacts indicates that the virus remains attenuated after passage through human hosts.

Individuals at high risk of severe varicella
There is only limited data from clinical trials available for *VARILRIX* (+4°C formulation) in individuals at high risk of severe varicella.
Vaccination may be considered in patients with selected immune deficiencies where the benefits outweigh the risks (e.g. asymptomatic HIV subjects, IgG subclass deficiencies, congenital neutropenia, chronic granulomatous disease, and complement deficiency diseases).
Immunocompromised patients who have no contraindication for this vaccination (see section *4.3 Contraindications*) may not respond as well as immunocompetent subjects, therefore some of these patients may acquire varicella in case of contact, despite appropriate vaccine administration. These patients should be monitored carefully for signs of varicella.
Should vaccination be considered in individuals at high risk of severe varicella, it is advised that:

- maintenance chemotherapy should be withheld one week before and one week after immunisation of patients in the acute phase of leukaemia. Patients under

radiotherapy should normally not be vaccinated during the treatment phase. Generally, patients are immunised when they are in complete haematological remission from their disease.
- the total lymphocyte count should be at least 1,200 per mm^3 or no other evidence of lack of cellular immune competence exists.
- vaccination should be carried out a few weeks before the administration of the immunosuppressive treatment for patients undergoing organ transplantation (e.g. kidney transplant).

Very few reports exist on disseminated varicella with internal organ involvement following vaccination with Oka varicella vaccine strain mainly in immunocompromised subjects.

VARILRIX must not be administered intravascularly or intradermally.

Phenylalanine content
The vaccine contains 331 micrograms of phenylalanine per dose. Phenylalanine may be harmful for individuals with phenylketonuria (PKU).

4.5 Drugs interactions

If tuberculin testing has to be done, it should be carried out before or simultaneously with vaccination since it has been reported that live viral vaccines may cause a temporary depression of tuberculin skin sensitivity. As this anergy may last up to a maximum of 6 weeks, tuberculin testing should not be performed within that period after vaccination to avoid false negative results.

In individuals who have received immunoglobulins or a blood transfusion, vaccination should be delayed for at least three months because of the likelihood of vaccine failure due to passively acquired varicella antibodies.

Salicylates should be avoided for 6 weeks after varicella vaccination as Reye's Syndrome has been reported following the use of salicylates during natural varicella infection.

Use with other vaccines

Healthy individuals
Clinical studies with varicella-containing vaccines support concomitant administration of *VARILRIX* with any of the following monovalent or combination vaccines: measles-mumps-rubella vaccine (MMR), diphtheria-tetanus-acellular pertussis vaccine (DTPa), reduced antigen diphtheria-tetanus-acellular pertussis vaccine (dTpa), Haemophilus influenzae type b vaccine (Hib), inactivated polio vaccine (IPV), hepatitis B vaccine (HBV), hexavalent vaccine (DTPa-HBV-IPV/Hib), hepatitis A vaccine (HAV), meningococcal serogroup C conjugate vaccine (MenC), meningococcal serogroups A, C, W and Y conjugate vaccine (MenACWY) and pneumococcal conjugate vaccine (PCV).

Different injectable vaccines should always be administered at different injection sites.

If a measles vaccine is not given at the same time as *VARILRIX* , there should be an interval of at least one month between the administration of these vaccines as the measles vaccine may lead to short-term suppression of the cellular immune response.

Individuals at high risk of severe varicella
VARILRIX should not be administered at the same time as other live attenuated vaccines. Inactivated vaccines may be administered in any temporal relationship to *VARILRIX*, given that no specific contraindication has been established. However, different injectable vaccines should always be administered at different injection sites.

4.6 Use in Special Populations

Pregnancy
Pregnant women should not be vaccinated with *VARILRIX*.

However, foetal damage has not been documented when varicella vaccines have been given to pregnant women.

Women of childbearing potential
Pregnancy should be avoided for one month following vaccination. Women intending to become pregnant should be advised to delay.

Breast-feeding
There are no data regarding use in breast-feeding women.
Due to the theoretical risk of transmission of the vaccine viral strain from mother to infant, *VARILRIX* is generally not recommended for breast-feeding mothers (see also *section 4.4 Special warnings and precautions for use*). Vaccination of exposed women with negative history of varicella or known to be seronegative to varicella should be assessed on an individual basis.

Fertility
No data available.

4.7 Effects on ability to drive and use machines

No studies on the effects of *VARILRIX* on the ability to drive and use machines have been performed. *VARILRIX* has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under *section 4.8 Undesirable Effects* may temporarily affect the ability to drive or use machines.

4.8 Undesirable Effects

Clinical trials

Healthy individuals

More than 7,900 individuals have participated in clinical trials evaluating the reactogenicity profile of the vaccine administered subcutaneously either alone or concomitantly with other vaccines.

The safety profile presented below is based on a total of 5369 doses of *VARILRIX* administered as monotherapy to children, adolescents and adults.

Adverse reactions reported are listed according to the following frequency:
Very common (≥1/10)
Common (≥1/100, <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)

Within each frequency grouping the adverse reactions are presented in the order of decreasing seriousness.

System organ class*	Frequency	Adverse Reaction
Infections and infestations	Uncommon	Upper respiratory infection, pharyngitis
Blood and lymphatic system disorders	Uncommon	Lymphadenopathy
Psychiatric disorders	Uncommon	Irritability
Nervous system disorders	Uncommon	Headache, somnolence
Eye disorders	Rare	Conjunctivitis
Respiratory, thoracic and mediastinal disorders	Uncommon	Cough, rhinitis
Gastrointestinal disorders	Uncommon	Nausea, vomiting
	Rare	Abdominal pain, diarrhoea
Skin and subcutaneous tissue disorders	Common	Rash
	Uncommon	Viral rash, pruritus
	Rare	Urticaria
Musculoskeletal and systemic disorders	Uncommon	Arthralgia, myalgia
General disorders and administration site conditions	Very common	Pain, erythema
	Common	Pyrexia (oral / axillary temperature ≥ 37.5 °C or rectal temperature ≥ 38.0 ºC) †, injection site swelling†
	Uncommon	Pyrexia (oral / axillary temperature> 39.0°C or rectal temperature> 39.5°C), fatigue, malaise

* According to MedDRA (Medical Dictionary for Regulatory Activities) terminology

† Injection site swelling and pyrexia were reported very commonly in studies conducted in adolescents and adults. Injection site swelling was also reported very commonly after the second dose in children under 13 years of age.

A trend for higher incidence of pain, erythema and injection site swelling after the second dose was observed as compared to the first dose.

No difference were seen in the reactogenicity profile between initially seropositive and initially seronegative subjects.

In a clinical trial, 328 children aged 11 to 21 months received GSK's combined measles, mumps, rubella and varicella vaccine (containing the same varicella strain as *VARILRIX*) either by subcutaneous or intramuscular route. A comparable safety profile was observed for both administration routes.

Individuals at high risk of severe varicella
There are limited data from clinical trials available in subjects at high risk of severe varicella. However, vaccine-associated reactions (mainly papulo-vesicular eruptions and pyrexia) are usually mild. As in healthy subjects, erythema, swelling and pain at the site of injection are mild and transient.

Post-marketing data

The following additional adverse reactions have been identified in rare occasions during post-marketing surveillance. Because they are reported voluntarily from a population of unknown size, a true estimate of frequency cannot be provided.

System organ class*	**Adverse reactions**
Infections and infestations	herpes zoster
Blood and lymphatic system disorders	thrombocytopenia
Immune system disorders	anaphylactic reaction, hypersensitivity
Nervous system disorders	encephalitis, cerebrovascular accident, seizure, cerebellitis, cerebellitis-like symptoms (including transient gait disturbance and transient ataxia)
Vascular disorders	vasculitis (including Henoch Schonlein purpura and Kawasaki syndrome)
Skin and subcutaneous tissue disorders	erythema multiforme

* According to MedDRA (Medical Dictionary for Regulatory Activities) terminology

4.9 Overdose

Cases of accidental administration of doses higher than the recommended dose of *VARILRIX* have been reported. Among these cases, the following adverse events were reported: lethargy and convulsions. In the other reported cases of overdose, there were no associated adverse events.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Viral vaccine, ATC code: J07BK01.

5.1 Mechanism of Action

VARILRIX produces an attenuated clinically inapparent varicella infection in susceptible subjects.
The presence of antibodies is accepted as evidence of protection, however, there is no established limit of protection for varicella disease.

5.2 Pharmacodynamic properties

Efficacy and effectiveness

The efficacy of GSK's Oka varicella vaccines in preventing confirmed varicella disease (by Polymerase Chain Reaction (PCR) or exposure to varicella case) has been evaluated in a large randomised multicountry clinical trial, which included GSK's combined measles-mumps-rubella vaccine (PRIORIX) as active control. The trial has been conducted in Europe where no routine varicella vaccination was implemented at that time. Children aged 12-22 months received one dose of *VARILRIX* or two doses of GSK's combined measles-mumps-rubella-varicella vaccine (*PRIORIX-TETRA*) six weeks apart. Vaccine efficacy against confirmed varicella of any severity and against moderate or severe confirmed varicella was observed after a primary follow-up period of 2 years (median duration 3.2 years). Persistent efficacy was observed in the same study during the long-term follow-up periods of 6 years (median duration 6.4 years) and 10 years (median duration 9.8 years). The data are presented in the Table below.

Group	Timing	Effectiveness against confirmed varicella of any severity	Efficacy against moderate or severe confirmed varicella
GSK's monovalent varicella (Oka) vaccine (*VARILRIX*) (1 dose) N =2,487	Year 2	65.4% (97.5% CI: 57. 2, 72.1)	90.7% (97.5 % CI:85.9, 93.9)
	Year 6 [(1)]	67.0% (95% CI: 61.8, 71.4)	90.3% (95% CI: 86.9, 92.8)
	10 years	67.2% (95% CI: 62.3; 71.5)	89.5% (95% CI: 86.1; 92.1)

GSK's combined measles, mumps, rubella and varicella (Oka) vaccine (Priorix-Tetra) (2 doses) N = 2,489	Year 2	94.9% (97.5% CI: 92.4, 96.6)	99.5% (97.5% CI: 97.5, 99.9)
	Year 6 [(1)]	95.0% (95% CI: 93.6, 96.2)	99.0% (95% CI: 97.7, 99.6)
	10 years	95.4% (95% CI: 94.0; 96.4)	99.1% (95% CI: 97.9; 99.6)

N: number of subjects enrolled and vaccinated

[(l)] descriptive analysis

In clinical trials, the majority of vaccinated subjects who were subsequently exposed to wild-type virus were either completely protected from clinical chickenpox or developed a milder form of the disease (i.e. low number of vesicles, absence of fever).

Effectiveness data, deriving from observation in different contexts (epidemic onset, case-control studies, observational studies, databases, models) suggest a higher level of protection and a decrease in the occurrence of cases of chickenpox following two doses of vaccine compared to a single dose.

The impact of one dose of *VARILRIX* in reducing varicella hospitalisations and ambulatory visits among children were respectively 81% and 87% overall.

Individuals at high risk of severe varicella

Patients suffering from leukaemia, patients under immunosuppressive treatment (including corticosteroid therapy) for malignant solid tumour, for serious chronic diseases (such as chronic renal failure, auto-immune diseases, collagen diseases, severe bronchial asthma) or following organ transplantation, are predisposed to severe natural varicella. Vaccination with the Oka-strain has been shown to reduce the complications of varicella in these patients.

Immune response after subcutaneous administration

Healthy individuals

In children aged 11 months to 21 months the seroresponse rate, when measured by ELISA 6 weeks after vaccination, was 89.6% after one vaccine dose and 100% after the second vaccine dose.

In children aged 9 months to 12 years the overall seroconversion rate, when measured by Immunofluorescence Assay (IFA) 6 weeks after vaccination, was >98% after one vaccine dose.

In children from 9 months to 6 years of age the seroconversion rate, when measured by IFA 6 weeks after vaccination, was 100% after a second vaccine dose. A marked increase

in antibody titers was observed following the administration of a second dose (5 to 26-fold increase of geometric mean titres).

In subjects 13 years and above the seroconversion rate, when measured by IFA 6 weeks after vaccination, was 100% after the second vaccine dose. One year after vaccination, all subjects tested were still seropositive.

Individuals at high risk of severe varicella

Limited data from clinical trials have shown immunogenicity in subjects at high risk of severe varicella.

Immune response after intramuscular administration

The immunogenicity of *VARILRIX* administered intramuscularly is based on a comparative study where 283 healthy children aged 11 to 21 months received GSK's combined measles, mumps, rubella and varicella vaccine (containing the same varicella strain as *VARILRIX*) either by subcutaneous or intramuscular route. Comparable immunogenicity was demonstrated for both administration routes.

5.3 Pharmacokinetic Properties

Evaluation of the pharmacokinetic properties is not required for vaccines.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

Non-clinical data reveal no special hazard for humans based on general safety tests performed in animals.

7. DESCRIPTION

The varicella vaccine (live) is a freeze-dried preparation presented as a monodose in 3 ml glass vial to be reconstituted with Water for Injection (WFI) diluent.
The WFI diluent used to reconstitute the lyophilised vaccine is presented as monodose in prefilled glass syringes (type 1), which meet the Ph. Eur. requirements for Glass containers for pharmaceutical use.

The vaccine is reconstituted by adding the entire content of the supplied container of diluent to the vial containing powder. The reconstituted vaccine is a clear peach to pink coloured liquid, free from visible particles.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

8.2 Shelf Life

24 months.

After reconstitution, it is recommended that the vaccine be injected as soon as possible.

However, it has been demonstrated that the reconstituted vaccine may be kept for up to 90 minutes at room temperature (25°C) and up to 8 hours in the refrigerator (2°C to 8°C). If not used within the recommended in-use storage timeframes and conditions, the reconstituted vaccine must be discarded.

8.3 Packaging Information

Powder in a single-dose glass vial (type I glass) with a stopper (bromobutyl rubber).
0.5 ml of solvent in a pre-filled syringe (type I glass) with plunger stopper (bromobutyl rubber) in pack sizes of 1 or 10.

Not all pack sizes may be marketed.

8.4 Storage and Handling Instructions

Store and transport refrigerated (2°C to 8°C).

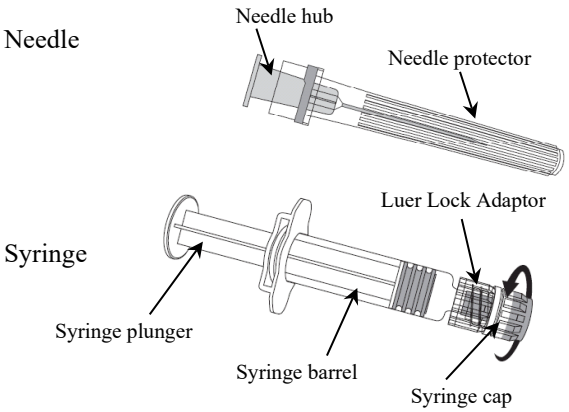
Store in the original package in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section *8.2 Shelf Life*.

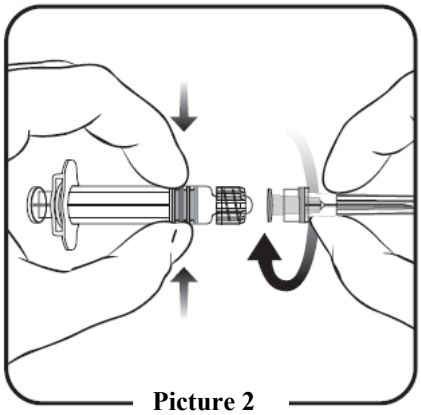
The solvent and the reconstituted vaccine should be inspected visually for any foreign particulate matter and/or abnormal physical appearance before administration. In the event of either being observed, do not administer the vaccine.

The vaccine must be reconstituted by adding the entire contents of the pre-filled syringe of solvent to the vial containing the powder.

To attach the needle to the syringe, carefully read the instructions given with pictures 1 and 2. However, the syringe provided with *VARILRIX* might be slightly different (without screw thread) than the syringe illustrated.
In that case, the needle should be attached without screwing.



Picture 1



Picture 2

Always hold the syringe by the barrel, not by the syringe plunger or the Luer Lock Adaptor (LLA), and maintain the needle in the axis of the syringe (as illustrated in picture 2). Failure to do this may cause the LLA to become distorted and leak.

During assembly of the syringe, if the LLA becomes detached, a new vaccine dose (new syringe and vial) should be used.

1. Unscrew the syringe cap by twisting it anticlockwise (as illustrated in picture 1).

Whether the LLA is rotating or not, please follow the steps below:

2. Attach the needle to the syringe by gently connecting the needle hub into the LLA and rotate a quarter turn clockwise until you feel it lock (as illustrated in picture 2).

3. Remove the needle protector, which may be stiff.

4. Add the solvent to the powder. The mixture should be well shaken until the powder is completely dissolved in the solvent.

The colour of the reconstituted vaccine may vary from clear peach to pink due to minor variations of its pH. This is normal and does not impair the performance of the vaccine. In the event of other variation being observed, do not administer the vaccine.

5. Withdraw the entire contents of the vial.

6. A new needle should be used to administer the vaccine. Unscrew the needle from the syringe and attach the injection needle by repeating step 2 above.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

9. PATIENT COUNSELLING INFORMATION

Registered Medical Practitioners may counsel their patients (and/or patients' caregiver as applicable) of the potential benefits and undesirable effects of vaccination with *VARILRIX*. Patients (and/or patients' caregiver) may also be informed about posology (including vaccination schedule if applicable), method of administration and storage/handling information of *VARILRIX* vaccine as applicable.

Registered Medical Practitioners may also choose to inform their patients (and/or patients' caregiver) about the special warnings and precautions for use, drug interactions, and any relevant contra-indications associated with *VARILRIX* vaccine.

10. DETAILS OF MANUFACTURER

Manufactured by:
M/s. GlaxoSmithKline Biologicals S.A.
89 Rue de l Institut - B-1330
Rixensart (Belgium)

For further information please contact:
GlaxoSmithKline Pharmaceuticals Limited.
Registered Office:
Dr. Annie Besant Road, Worli
Mumbai 400 030, India.

11. DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE

Marketing Authorization Holder: GlaxoSmithKline Pharmaceuticals Ltd.,

Marketing Authorization Details: File No. 12-70/96-DC Part (I) dt. 19-June-1998

12. DATE OF REVISION

05-September-2024

*Version VRX/PI/IN/20**24**/0**1***

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