# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Engerix B 10 micrograms/0.5 ml Suspension for injection in pre-filled syringe Hepatitis B (rDNA) vaccine (adsorbed) (HBV)

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (0.5 ml) contains:

Hepatitis B surface antigen [1, 2] 10 micrograms

[1]Adsorbed on aluminium hydroxide, hydrated Total: 0.25 milligrams $Al^{3+}$
[2]Produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Suspension for injectionin pre-filled syringe.
Turbid white suspension.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

ENGERIX B is indicated in neonates, infants, children and adolescents up to and including 15 years of age for active immunisation against hepatitis B virus infection (HBV) caused by all known subtypes in non-immune subjects. The categories within the population to be immunised are determined on the basis of official recommendations.

It can be expected that hepatitis D will also be prevented by immunisation with ENGERIX B as hepatitis D (caused by the delta agent) does not occur in the absence of hepatitis B infection.

### 4.2 Posology and method of administration

**Posology**

*Dosage*

ENGERIX B (10 microgram/0.5 ml) is intended for use in subjects up to and including 15 years of age, including neonates.
ENGERIX B (20 microgram/1 ml) is intended for use in subjects 16 years of age and above.

However, ENGERIX B (20 microgram/1 ml) can also be used in subjects from 11 years up to and including 15 years of age as a 2-dose schedule in situations when there is a low risk of hepatitis B infection during the vaccination course and when compliance with the complete vaccination course can be assured (see section 5.1 and SmPC for ENGERIX B (20 microgram/1 ml).

*Primary Immunisation schedules*

- Subjects up to and including 15 years of age:

Two primary immunisation schedules can be recommended:

A 0, 1, 6 months schedule which gives optimal protection at month 7 and produces high antibody concentrations.

An accelerated schedule, with immunisation at 0, 1 and 2 months, which will confer protection more quickly and is expected to provide better patient compliance. With this schedule, a fourth dose should be administered at 12 months to assure long term protection as antibody concentrations after the third dose are lower than those obtained after the 0, 1, 6 months schedule. In infants, this schedule will allow for simultaneous administration of hepatitis B with other childhood vaccines.

- Patients with renal insufficiency including patients undergoing haemodialysis:

Patients with renal insufficiency, including patients undergoing haemodialysis, have a reduced immune response to hepatitis B vaccines. Either the 0, 1, 2 and 12 months or the 0, 1, 6 months schedule of ENGERIX B (10 microgram/0.5 ml) can be used. Based on adult experience, vaccination with a higher dosage of antigen may improve the immune response. Consideration should be given to serological testing following vaccination. Additional doses of vaccine may be needed to ensure a protective anti-HBs level $^{3}$ 10 mIU/ml.

- Known or presumed exposure to HBV:

In circumstances where exposure to HBV has recently occurred (e.g. needlestick with contaminated needle) the first dose of ENGERIX B can be administered simultaneously with HBIg which however must be given at a separate injection site (see section 4.5). The 0, 1, 2-12 months immunisation schedule should be advised.

- Neonates born of mothers who are HBV carriers:

The immunisation with ENGERIX B (10 microgram/0.5 ml) of these neonates should start at birth, and two immunisation schedules have been followed. Either the 0, 1, 2 and 12 months or the 0, 1 and 6 months schedule can be used; however, the former schedule provides a more rapid immune response. When available, hepatitis B immune globulins (HBIg) should be given simultaneously with ENGERIX B at a separate injection site as this may increase the protective efficacy.

These immunisation schedules may be adjusted to accommodate local immunisation practices with regard to the recommended age of administration of other childhood vaccines.

*Booster dose*

Current data do not support the need for booster vaccination among immunocompetent subjects who have responded to a full primary vaccination course.

However, in immunocompromised subjects (e.g. subjects with chronic renal failure, haemodialysis patients, HIV positive subjects), boosters should be administered to maintain anti-HBs antibody concentrations equal or higher than the accepted protective level of 10 mIU/ml. For these immunocompromised subjects, post-vaccination testing every 6-12 month is advised.

National recommendations on booster vaccination should be considered.

*Interchangeability of hepatitis B vaccines*

See section 4.5.

**Method of administration**

ENGERIX B should be injected intramuscularly in the deltoid region in children or in the anterolateral thigh in neonates, infants and young children.

Exceptionally the vaccine may be administered subcutaneously in patients with thrombocytopenia or

**4.3 Contraindications**

ENGERIX B should not be administered to subjects with known hypersensitivity to the active substances or to any of the excipients listed in section 6.1, or to subjects having shown signs of hypersensitivity after previous ENGERIX B administration.

As with other vaccines, the administration of ENGERIX B should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection, however, is not a contraindication for immunisation.

**4.4 Special warnings and precautions for use**

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Precautions for use
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 disturbance, paraesthesia and tonic-clonic limb movements during recovery. It is important that procedures are in place to avoid injury from faints.

ENGERIX B Junior should not be administered in the buttock or intradermally since this may result in a lower immune response.

ENGERIX B Junior should under no circumstances be administered intravascularly.

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

Protection
Because of the long incubation period of hepatitis B it is possible for unrecognised infection to be present at the time of immunisation. The vaccine may not prevent hepatitis B infection in such cases.

The vaccine will not prevent infection caused by other pathogens known to infect the liver such as hepatitis A, hepatitis C and hepatitis E viruses.

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

A number of factors have been observed to reduce the immune response to hepatitis B vaccines. These factors include male gender, obesity, smoking, route of administration, and some chronic underlying diseases. Consideration should be given to serological testing of those subjects who may be at risk of not achieving seroprotection following a complete course of

ENGERIX B. Additional doses may need to be considered for persons who do not respond or have a sub-optimal response to a course of vaccinations.

Special population
Patients with chronic liver disease or with HIV infection or hepatitis C carriers should not be precluded from vaccination against hepatitis B. The vaccine could be advised since HBV infection can be severe in these patients: the HB vaccination should thus be considered on a case by case basis by the physician. In HIV infected patients, as also in patients with renal insufficiency including patients undergoing haemodialysis and persons with an impaired immune system, adequate anti-HBs antibody concentrations may not be obtained after the primary immunisation course and such patients may therefore require administration of additional doses of vaccine.

Preterm infants
The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunization series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity.
As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

Sodium content
This vaccine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium free'.

**4.5 Interaction with other medicinal products and other forms of interaction**

The simultaneous administration of ENGERIX B and a standard dose of HBIg does not result in lower anti-HBs antibody concentrations provided that they are administered at separate injection sites.

ENGERIX B can be given concomitantly with *Haemophilus influenzae* b, BCG, hepatitis A, polio, measles, mumps, rubella, diphtheria, tetanus and pertussis vaccines.

ENGERIX B can be given concomitantly with Human Papillomavirus (HPV) vaccine.
Administration of ENGERIX B at the same time as Cervarix (HPV vaccine) has shown no clinically relevant interference in the antibody response to the HPV antigens. Anti-HBs geometric mean antibody concentrations were lower on co-administration, but the clinical significance of this observation is not known since the seroprotection rates remain unaffected. The proportion of subjects reaching anti-HBs ≥ 10mIU/ml was 97.9% for concomitant vaccination and 100% for ENGERIX B alone.

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

ENGERIX B may be used to complete a primary immunisation course started either with plasma-derived or with other genetically-engineered hepatitis B vaccines, or, if it is desired to administer a booster dose, it may be administered to subjects who have previously received a primary immunisation course with plasma-derived or with other genetically-engineered hepatitis B vaccines.

It may be expected that in patients receiving immunosuppressive treatment or patients with immunodeficiency, an adequate immune response may not be elicited (see section 4.4).

**4.6 Fertility, pregnancy and lactation**

The effect of the HBsAg on foetal development has not been assessed.

However, as with all inactivated viral vaccines one does not expect harm for the foetus. ENGERIX B should be used during pregnancy only when clearly needed, and the possible advantages outweigh the possible risks for the foetus.

Breast-feeding
The effect on breastfed infants of the administration of ENGERIX B to their mothers has not been evaluated in clinical studies, as information concerning the excretion into the breastmilk is not available.

No contraindication has been established.

Fertility

ENGERIX B has not been evaluated in fertility studies.

**4.7 Effects on ability to drive and use machines**

ENGERIX B has no or negligible influence on the ability to drive and use machines.

**4.8 Undesirable effects**

**Summary of the safety profile**

The safety profile presented below is based on data from 5329 subjects followed in 23 studies.

The current formulation of ENGERIX B does not contain thiomersal (an organomercuric compound).
The following undesirable effects have been reported following the use of the thiomersal containing formulations as well as the thiomersal free formulation.

In one clinical study conducted with the current formulation (thiomersal free formulation), the incidence of pain, redness, swelling, drowsiness, irritability, loss of appetite and fever was comparable to the incidence observed in the clinical studies conducted with former thiomersal containing vaccine formulations.

**Tabulated summary of adverse reactions**

| System Organ Class | Frequency | Adverse reactions |
|---|---|---|
| **Clinical trials** | | |
| Blood and lymphatic system disorders | Rare | Lymphadenopathy |
| Metabolism and nutrition disorders | Common | Appetite lost |
| Psychiatric disorders | Very common | Irritability |
| Nervous system disorders | Very common | Headache |
| | Common | Drowsiness |
| | Uncommon | Dizziness |
| | Rare | Paraesthesia |
| Gastrointestinal disorders | Common | Gastrointestinal symptoms (such as nausea, vomiting, diarrhoea, abdominal pain) |
| Skin and subcutaneous tissue disorders | Rare | Urticaria, pruritus, rash |
| Musculoskeletal and connective tissue disorders | Uncommon | Myalgia |
| | Rare | Arthralgia |
| General disorders and administration site conditions | Very common | Pain and redness at injection site, fatigue |
| | Common | Fever (≥37.5°C), malaise, swelling at injection site, injection site reaction (such as induration) |
| | Uncommon | Influenza-like illness |
| **Post-marketing surveillance** | | |
| Infections and infestations | Not known (cannot be estimated | Meningitis |

| | | |
|---|---|---|
| | from the available data) | |
| Blood and lymphatic system disorders | Not known (cannot be estimated from the available data) | Thrombocytopenia |
| Immune system disorders | Not known (cannot be estimated from the available data) | Anaphylaxis, allergic reactions including anaphylactoid reactions and mimicking serum sickness |
| Nervous system disorders | Not known (cannot be estimated from the available data) | Encephalitis, encephalopathy, convulsions, paralysis, neuritis (including Guillain-Barré syndrome, optic neuritis and multiple sclerosis), neuropathy, hypoaesthesia |
| Vascular disorders | Not known (cannot be estimated from the available data) | Vasculitis, hypotension |
| Respiratory thoracic and mediastinal disorders | Not known (cannot be estimated from the available data) | Apnoea in very premature infants (≤ 28 weeks of gestation) (see section 4.4) |
| Skin and subcutaneous tissue disorders | Not known (cannot be estimated from the available data) | Erythema multiforme, angioneurotic oedema, lichen planus |
| Musculoskeletal and connective tissue disorders | Not known (cannot be estimated from the available data) | Arthritis, muscular weakness |

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

**4.9 Overdose**

Cases of overdose have been reported during post-marketing surveillance. Adverse events reported following overdosage were similar to those reported with normal vaccine administration.

**5 PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Hepatitis B vaccine, ATC code: J07BC01

**Mechanism of action**

ENGERIX B induces specific humoral antibodies against HBsAg (anti-HBs antibodies). Anti-HBs antibody concentrations $^{3}$10 mIU/ml correlate with protection to HBV infection.

**Pharmacodynamic effects**

Subjects with increased risk of HBV exposure

In field studies, a protective efficacy between 95% and 100% was demonstrated in neonates, children and adults at risk.

In healthy subjects in high risk area, one month after the last vaccine dose, a 95% protective efficacy (serum anti HBs IgG ≥ 10 mIU/ml) was demonstrated in neonates of HBeAg positive mothers, immunised according to the 0, 1, 2 and 12 month or 0, 1 and 6 month schedules without concomitant administration of hepatitis B immunoglobulin (HBIg) at birth. However, simultaneous administration of HBIg and vaccine at birth increased the protective efficacy to 98%.

Neonates born to mothers who were hepatitis B virus carriers (HBsAg positive with or without HBeAg) and who did not receive HBIg at birth received a challenge dose of Engerix B twenty years after primary vaccination (3-dose or 4-dose schedules). The seroprotection rate before and after the challenge dose has been evaluated:

| **Seroprotection rate** | **N** | **n** | **%** | **95% CI** | |
|---|---|---|---|---|---|
| | | | | **LL** | **UL** |
| Pre-challenge | 72 | 39 | 54.2 | 42.0 | 66.0 |
| Post-challenge | 75 | 74 | 98.7 | 92.8 | 100 |

N = number of subjects with available results
n = number of subjects with concentration equal to or above 10mIU/ml
% = percentage of subjects with concentration equal to or above 10mIU/ml
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = at the time of administration of the challenge dose / POST = one month after challenge dose

The anamnestic response according to the pre-challenge serostatus was also evaluated:

| | **Anamnestic response** | | | | |
|---|---|---|---|---|---|
| | | | | **95% CI** | |
| **Pre-challenge status** | **N** | **n** | **%** | **LL** | **UL** |
| Subjects < 10 mIU/ml | 33 | 31 | 93.9 | 79.8 | 99.3 |
| Subjects ≥ 10 mIU/ml | 39 | 39 | 100 | 91.0 | 100 |
| Total | 72 | 70 | 97.2 | 90.3 | 99.7 |
| | | | | | |

Stratification based on last available time point prior to challenge dose:

- subjects <10 mIU/ml = subjects with antibody concentration <10 mIU/ml prior to the challenge dose
- subjects ≥10 mIU/ml = subjects with antibody concentration ≥10 mIU/ml prior to the challenge dose Anamnestic response is defined as:
- anti-HBs antibody concentrations ≥ 10 mIU/ml in subjects who were seronegative before the challenge dose, or
- an increase in anti-HBs antibody concentrations by at least 4-fold in subjects who were seropositive before the challenge dose.N = number of subjects with both pre- and post-vaccination results availablen = number of responders% = percentage of responders95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit

General paediatric population:

- Seroprotection rates in subjects up to and including 15 years of age: The Table below summarizes seroprotection rates (i.e. percentages of subjects with anti-HBs antibody concentrations ³ 10 mIU/ml) obtained in clinical studies with the different schedules mentioned in Posology:

| Population | Schedule | Seroprotection rate |
|---|---|---|
| Healthy subjects up to and including 15 years of age | 0, 1, 6 months | at month 7: ³ 96 % |
| | 0, 1, 2 – 12 months | at month 1: 15 %<br>at month 3: 89 %<br>at month 13: 95.8 % |

The data in the above Table were generated with thiomersal containing vaccines. Two additional clinical studies conducted with the current formulation of ENGERIX B, which does not contain thiomersal, among healthy infants and adults, elicit similar seroprotection rates as compared to former thiomersal containing formulations of ENGERIX B.

- Persistence of immune response in subjects from 11 years up to and including 15 years of age:

The long-term immune response was assessed in a clinical trial in subjects from 11 years up to and including 15 years of age at the time of primary vaccination. Seroprotection rates (i.e. percentages of subjects with anti-HBs antibody concentrations ³ 10 mIU/ml) obtained in a comparative study with the two different dosages and schedules were evaluated up to 66 months after the first dose of the primary vaccination and are presented in the Table below (ATP cohort for efficacy):

| **Vaccination schedule** | **Months after the first vaccine dose** | | | | | | |
|---|---|---|---|---|---|---|---|
| | **2** | **6** | **7** | **30** | **42** | **54** | **66** |
| | **Seroprotection rate** | | | | | | |
| ENGERIX B (10 microgram/0.5 ml) (0, 1, 6 months) | 55.8 | 87.6 | 98.2* | 96.9 | 92.5 | 94.7 | 91.4 |
| ENGERIX B (20 microgram/1 ml) (0, 6 months) | 11.3 | 26.4 | 96.7* | 87.1 | 83.7 | 84.4 | 79.5 |

*At month 7, 97.3% and 88.8% of subjects aged 11 to 15 years vaccinated with ENGERIX B (10 microgram/0.5 ml) (0, 1, 6 months schedule) or ENGERIX B (20 microgram/1 ml) (0, 6 months schedule) respectively developed anti-HBs antibody concentrations ≥ 100 mIU/ml. Geometric Mean Concentrations (GMC) were 7238 mIU/ml and 2739 mIU/ml respectively.

All subjects in both vaccine groups (N=74) received a challenge dose 72 to 78 months after primary vaccination. One month later, all subjects mounted an anamnestic response with a GMC increase of 108 and 95fold from the pre-to the post challenge time points in the 2-dose and 3-dose priming schedule respectively and were shown to be seroprotected. These data suggest that immune memory was induced in all subjects who responded to primary vaccination, even among those who had lost seroprotection at Month 66.

- Persistence of immune response and rechallenge of subjects aged 15 to 16 years 14 years after primary vaccination: Seroprotection rates before and after a challenge dose have been evaluated in subjects aged 15 to 16 years who were vaccinated with 3 doses of ENGERIX-B during the first two years of life:

| **Seroprotection rate** | **N** | **n** | **%** | **95% CI** | |
|---|---|---|---|---|---|
| | | | | **LL** | **UL** |
| Pre-challenge | 292 | 191 | 65.4 | 59.6 | 70.9 |
| Post-challenge | 292 | 286 | 97.9 | 95.6 | 99.2 |

N = number of subjects with available results
n = number of subjects with concentration equal to or above 10mIU/ml
% = percentage of subjects with concentration equal to or above 10mIU/ml
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = prior to the challenge dose / POST= one month after challenge dose

Anamnestic response has been evaluated according to pre-challenge serostatus in subjects aged 15 to 16 years who were vaccinated with 3 doses of ENGERIX-B during the first two years of life:

| | **Anamnestic response** | | | | |
|---|---|---|---|---|---|
| | | | | **95% CI** | |
| **Pre-challenge status** | **N** | **n** | **%** | **LL** | **UL** |
| Subjects < 10 mIU/ml | 101 | 95 | 94.1 | 87.5 | 97.8 |
| Subjects ≥ 10 mIU/ml | 190 | 187 | 98.4 | 95.5 | 99.7 |
| Total | 291 | 282 | 96.9 | 94.2 | 98.6 |

Stratification based on last available time point prior to booster dose:

- subjects <10 mIU/ml = subjects with antibody concentration <10 mIU/ml prior to the challenge dose
- subjects ≥10 mIU/ml = subjects with antibody concentration ≥10 mIU/ml prior to the challenge dose Anamnestic response is defined as:
- anti-HBs antibody concentrations ≥ 10 mIU/ml in subjects who were seronegative before the challenge dose, or
- an increase in anti-HBs antibody concentrations by at least 4-fold in subjects who were seropositive before the challenge dose.N = number of subjects with both pre- and post-vaccination results availablen = number of responders% = percentage of responders95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit

The primary endpoint of the study, defined as the percentage of subjects with anti-HBs antibody concentrations ≥ 100 mIU/mL one month after the challenge dose, was calculated at 90.8% (95% CI: 86.8; 93.8). The anti-HBs antibody GMC increased by 156-fold (from 26.5 to 4134.9 mIU/mL) as a response to the challenge dose.

Similar data with respect to seroprotection rates and anamnestic response were obtained in subjects (N=279) aged 12 - 13 years.

Reduction in the incidence of hepatocellular carcinoma in children:

A clear link has been demonstrated between hepatitis B infection and the occurrence of hepatocellular carcinoma (HCC). The prevention of hepatitis B by vaccination results in a reduction of the incidence of HCC, as has been observed in Taiwan in children aged 6-14 years.

**5.2 Pharmacokinetic properties**

Not applicable.

**5.3 Preclinical safety data**

The preclinical safety data satisfy the requirements of the WHO.

**6 PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Sodium chloride
Disodium phosphate dihydrate
Sodium dihydrogen phosphate
Water for injections

For adsorbent, see section 2.

**6.2 Incompatibilities**

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

**6.3 Shelf life**

3 years.

**6.4 Special precautions for storage**

Store in a refrigerator (2°C - 8°C).
Store in the original package.
Do not freeze.
Stability data indicate that ENGERIX B is stable at temperatures up to 37°C for 3 days or up to 25°C for 7 days. These data are intended to guide healthcare professionals in case of temporary temperature excursion only.

**6.5 Nature and contents of container**

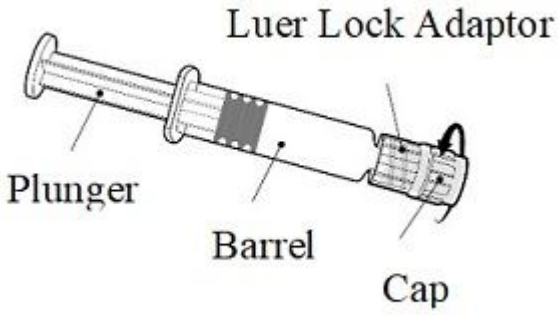
0.5 ml of suspension in a pre-filled syringe (type I glass) with a plunger stopper (butyl rubber) and with a rubber tip cap.
Pack sizes of 1 and 10, with or without needles.

The tip cap and rubber plunger stopper of the pre-filled syringe are made with synthetic rubber.

**6.6 Special precautions for disposal and other handling**

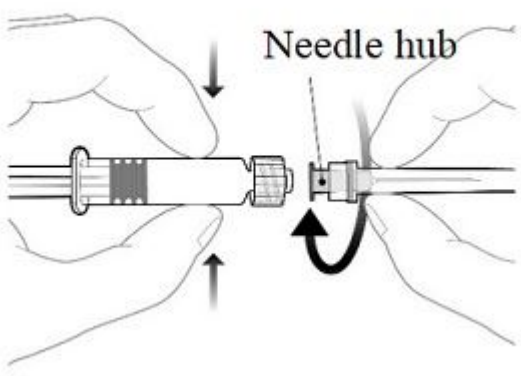
Upon storage, the content may present a fine white deposit with a clear colourless supernatant. Once shaken the vaccine is slightly opaque.
The vaccine should be inspected visually for any foreign particulate matter and/or abnormal physical appearance prior to administration. In the event of either being observed, do not administer the vaccine.
The entire contents of a mono-dose container must be withdrawn and should be used immediately.

<u>Instructions for the pre-filled syringe</u>




Hold the syringe by the barrel, not by the plunger.

Unscrew the syringe cap by twisting it anticlockwise.




To attach the needle, connect the hub to the Luer Lock Adaptor and rotate a quarter turn clockwise until you feel it lock.

Do not pull the syringe plunger out of the barrel. If it happens, do not administer the vaccine.

Disposal

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

## 7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

## 8 MARKETING AUTHORISATION NUMBER

PA1077/023/001

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 June 1998

Date of last renewal: 14November 2008

## 10 DATE OF REVISION OF THE TEXT

May 2023