NEW ZEALAND DATA SHEET

1. PRODUCT NAME

ENGERIX-B 20 micrograms/mL, suspension for injection.

ENGERIX-B paediatric 10 micrograms/0.5 mL, suspension for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ENGERIX-B paediatric dose: 10 microgram (µg) dose vaccine

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

ENGERIX-B: 20 microgram (µg) dose vaccine

1 dose (1 mL) contains:

Hepatitis B surface antigen[1, 2]	20 micrograms
[1]Adsorbed on aluminium hydroxide, hydrated	Total: 0.50 milligrams Al^{3+}

[2]Produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology

The vaccine is highly purified, and meets the WHO requirements for recombinant hepatitis B vaccines. No substances of human origin are used in its manufacture.

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Suspension for injection.
ENGERIX-B is a turbid white suspension. Upon storage, a fine white deposit with a clear colourless supernatant may be observed.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ENGERIX-B is indicated for active immunisation against hepatitis B virus infection. As part of the national immunisation schedule, the New Zealand Ministry of Health* recommend all infants, unvaccinated children up to the age of 16 years, and household and sexual contacts of known hepatitis B carriers receive a primary course of vaccination against hepatitis B.

Immunisation is also recommended for seronegative persons who are at substantial risk and have been demonstrated or judged to be susceptible to the hepatitis B virus (HBV). Groups identified at increased risk of acquiring HBV infection include:

- **Infants born to carrier (HBsAg-positive) mothers**
- **Infants (born to HBsAg-negative mothers) and young children (under 10 years) in communities with a hepatitis B carrier rate over 2%** including indigenous peoples of the Western Pacific, such as Maori and Pacific Islands people, and individuals from most countries in Asia, Africa, Oceania, Central and South America, Eastern Europe, and the Mediterranean region.
- **Susceptible sexual contacts.** Risk occurs in susceptible (anti-HBs negative) partners of HBV carriers and patients with acute hepatitis B. Susceptible clients of STD (sexually transmitted disease) clinics, and sexually active male homosexuals are also at increased risk of infection
- **Injecting drug users**
- **Haemodialysis patients**
- **Patients frequently receiving certain blood products** especially patients with clotting disorders receiving factor VIII or IX concentrates
- **Hepatitis C virus carriers not immunised against hepatitis B.**
- **Staff and residents of facilities for the intellectually disabled**, including both residential and non-residential care of this group.
- **Close residential contacts of deinstitutionalised intellectually disabled individuals who are hepatitis B virus carriers;** where these individuals behave aggressively or have medical problems that increase the risk of exposing others to their blood or serous secretions, the vaccine may also be offered to household and classroom contacts
- **Staff and inmates of correctional facilities**
- **Health care workers and embalmers** All staff directly involved in patient care, embalming, or in the handling of human blood or tissue should be vaccinated
- **Household contacts (other than sexual partners) of acute and chronic hepatitis B cases and carriers**
- **Others in whom vaccination may be justified** include police and members of the armed forces, depending on the risks of exposure associated with assigned duties. Short-term tourists or business travellers to areas of high HBV endemicity may consider vaccination; however the risk of hepatitis B is generally minimal provided exposure through sexual contact, injecting drug use, tattooing or ear piercing is avoided. Long term visitors to areas of high HBV endemicity, who anticipate close personal contact with local residents should be vaccinated.

As hepatitis D (caused by delta agent) does not occur in the absence of hepatitis B infection, it can be expected that hepatitis D may be prevented by vaccination with ENGERIX-B. The vaccine will not protect against infection caused by hepatitis A, hepatitis C and hepatitis E viruses, and other pathogens known to infect the liver.

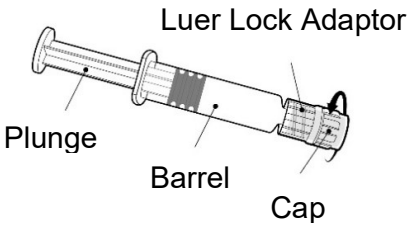
Vaccination against hepatitis B is expected in the long term to reduce not only the overall incidence of hepatitis B but also chronic complications such as chronic active hepatitis and cirrhosis. It may also reduce the incidence of primary hepatocellular carcinoma.

4.2 Dose and method of administration

The vaccine is ready for use. It must be well shaken before use, since a fine white deposit with a clear colourless supernatant may form upon storage. After shaking the vaccine is a slightly opaque, white suspension. Discard if the contents of the vial appear otherwise. All parenteral drug

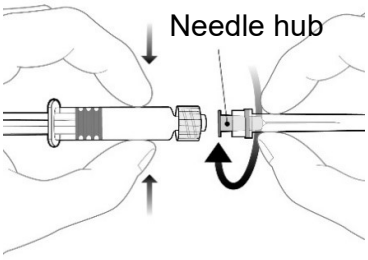
and vaccine products should be inspected visually prior to administration for discolouration or particulate matter.

Instructions for the pre-filled syringe



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.

Dose

The vaccine can be administered at any age from birth onwards.

Adults and adolescents over 15 years:

A dose of 20 µg of antigen protein in 1 mL suspension is recommended.

Adolescents:

In adolescents from the age of 10 years, and up to and including 15 years, a 10 µg dose can be recommended provided the immunisation is carried out in the 0, 1 and 6 months schedule, in circumstances which will ensure compliance to the full vaccination course. If compliance cannot be assured, then a 20 µg dose should be used to increase the proportion of subjects protected after the first and second doses.

Neonates, infants and younger children:

A dose of 10 µg of antigen protein in 0.5 mL suspension is recommended for neonates, infants and children up to 10 years of age although a dose of 20 µg may also be used when a paediatric presentation is not available.

In neonates and infants, maternally transferred antibodies do not interfere with the active immune response to the vaccine.

Method of administration

ENGERIX-B should be injected intramuscularly.

In adults the injection should be given in the deltoid region but it may be preferable to inject ENGERIX-B in the anterolateral thigh in neonates and infants because of the small size of their deltoid muscle. Exceptionally the vaccine may be administered subcutaneously in patients with thrombocytopenia or severe bleeding tendencies (e.g. haemophiliacs).
When administered concurrently with other vaccines, ENGERIX-B should be administered at a separate injection site.

ENGERIX-B must not be given intravenously.

Vaccination Schedule:

It is suggested that in conjunction with the ENGERIX-B vaccination schedule recommendations, the New Zealand Ministry of Health Immunisation Guidelines* on hepatitis B be consulted prior to use of the vaccine.

Primary vaccination:

This consists of three intramuscular doses of vaccine according to either of three different schedules:

In areas of low risk of infection:

- 1st dose: At elected date
- 2nd dose: 1 month later
- 3rd dose: 6 months from the date of the first dose.

In areas of high risk of infection:

- 1st dose: At elected date
- 2nd dose: 1 month later
- 3rd dose: 2 months from the date of the first dose.

Use in exceptional circumstances in adults (e.g. travellers commencing hepatitis B primary vaccination within one month of departure):

- 1st dose: At elected date
- 2nd dose: 7 days later
- 3rd dose: 21 days from the date of the first dose.

The two accelerated vaccination schedules of 0, 1 and 2 months or 0, 7 and 21 days may be used in circumstances where more rapid protection is required (e.g. contacts of carriers, and immunisation of travellers). However, as higher seroprotective rates are observed following the 0, 1, 2 month schedule, it is recommended the 0, 7, 21 day schedule be administered only in exceptional circumstances (e.g. travellers commencing hepatitis B primary vaccination within one month of departure). Since the peak antibody levels reached after these shorter schedules of primary vaccination are lower compared to the 0, 1 and 6 month schedule, it is recommended that

a fourth dose (booster) be given at 12 months after the first dose of vaccine. A 20 µg dose should be used with these accelerated schedules.

Booster Dose

Until now, it is not known whether individuals who have responded to the vaccine will require booster doses to ensure long term protection or whether natural boosting without symptoms and chronic infection will occur when vaccinees with anti-HBs titers below the protective level of 10 IU/L are exposed to virus.

Until such time as there is sufficient evidence to clarify the situation, it would seem wise to recommend a booster dose when the anti-HBs level falls below 10 IU/L.

The timing for a booster dose will depend upon the anti-HBs level reached after the primary course of vaccination. From available data the following general recommendations for the booster can be made:

1. After 0, 1, 6 month primary vaccination schedule. A booster dose after this primary course of vaccination will, on average, probably not be required earlier than five years later.

2. After 0, 1, 2 month or 0, 7, 21 day primary vaccination schedule. Since the peak antibody levels reached after these shorter schedules of primary vaccination are lower (compared to the 0, 1 6 month schedule), it is recommended that a booster dose be given at 12 months after the first dose of vaccine. The next booster will probably not be required before another eight years.

Neonates born to HBV carrier mothers

The recommended treatment regimen for infants born to HBsAg+ and HBsAg+/eAg+ mothers is as follows:

	Vaccine Dose	At birth	1 month*	2 months* OR 6 months*
ENGERIX-B vaccine	10 µg	0.5 mL	0.5 mL	0.5 mL
Hepatitis B Immunoglobulin	-	100 IU	-	-

* after first dose

Infants born to HBsAg+ and HBsAg+/eAg+ mothers may be administered either a 0, 1, 2 month or 0, 1, 6 month primary schedule, however the 0, 1, 2 month schedule elicits a more rapid immune response. The first dose of vaccine and immunoglobulin should be given within 24 hours of birth at separate sites.

Testing for HBsAg and anti-HBs is suggested at 12-15 months of age. If HBsAg is not detectable and anti-HBs is present, the child has been protected.

Immunocompromised Patients

The basic vaccination course recommended for chronic haemodialysis patients and other subjects who have an impairment of their immune system is four doses of 40 µg according to the following schedule:

- 1st dose: at elected date

- 2nd dose: 1 month later
- 3rd dose: 2 months from the date of the first dose.
- 4th dose: 6 months from the date of the first dose.

The anti-HBs titer of such patients should be checked annually and a booster dose recommended when it is close to the protective level of 10 IU/L. ENGERIX-B booster doses of 40 µg (2 x 20 µg) are recommended.

Post-Exposure Prophylaxis

There are no adequately controlled studies on the effectiveness of hepatitis B immunoglobulin administration, along with the vaccine, in adults and older children exposed to hepatitis B virus through 1) needlestick, ocular or mucous membrane exposure to blood known or presumed to contain HBsAg; 2) human bites by known or presumed HBsAg carriers that penetrate the skin; 3) following intimate sexual contact with known or presumed HBsAg carriers.

Hepatitis B immunoglobulin (human) (400 IU for adults) should be given intramuscularly as soon as possible, preferably within 24 hours of exposure. ENGERIX-B should be given at a separate site within 7 days and then at 1 month and 2 months. Passive immunisation will not interfere with active response to ENGERIX-B.

4.3 Contraindications

ENGERIX-B should not be administered to subjects with known hypersensitivity to any component of the vaccine, or to subjects having shown signs of hypersensitivity after previous ENGERIX-B administration.

4.4 Special warnings and precautions for use

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.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

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 agents such as hepatitis A, hepatitis C and hepatitis E and other pathogens known to infect the liver.

The immune response to hepatitis B vaccines is related to a number of factors, including older age, male gender, obesity, smoking habits and route of administration. In subjects who may respond less well to the administration of the hepatitis B vaccines (e.g. more than 40 years of age etc.), additional doses may be considered.

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

ENGERIX-B should under no circumstances be administered intravenously.

Patients with chronic liver disease (e.g. alcoholic liver disease, chronic biliary cirrhosis, chronic active hepatitis, etc.) should not be precluded from vaccination against hepatitis B. In these patients, hepatitis B vaccination should be considered on a case by case basis by the physician.

In haemodialysis patients, HIV infected patients and persons with an impaired immune system, adequate anti-HBs antibody titers may not be obtained after the primary immunisation course and such patients may therefore require administration of additional doses of vaccine.

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

The potential risk of apnoea and the need for respiratory monitoring for 48-72 hours 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.

As with any vaccine, a protective immune response may not be elicited in all vaccinees (see section 5.1 Pharmacodynamic properties).

4.5 Interaction with other medicines 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 titres provided that they are administered at separate injection sites.

ENGERIX-B can be given concomitantly with BCG, DTP, DT and/or polio vaccines, if this fits conveniently in an immunisation scheme recommended by the New Zealand Ministry of Health.

ENGERIX-B can be administered together with measles-mumps-rubella vaccines, Haemophilus influenzae b vaccine and hepatitis A vaccine.

ENGERIX-B can be given concomitantly with Human Papillomavirus (HPV) vaccine (CERVARIX).

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 ≥ 10 mLU/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 as a booster dose in subjects who have previously received a primary immunisation course with plasma-derived or with other genetically-engineered hepatitis B vaccines.

4.6 Fertility, pregnancy and lactation

Pregnancy

Adequate human data on use during pregnancy and adequate animal reproduction studies are not available.

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

Adequate human data on use during lactation and adequate animal reproduction studies are not available.

No contraindication has been established.

Fertility

ENGERIX-B has not been evaluated in fertility studies.

4.7 Effects on the ability to drive and use machines

The vaccine is unlikely to produce an effect on the ability to drive and use machines.

4.8 Undesirable effects

Clinical Trials Experience

ENGERIX-B is generally well tolerated.

The safety profile presented below is based on data from more than 5300 subjects.

Frequencies are reported as:

Very common: ≥ 1/10
Common: ≥1/100, <1/10
Uncommon: ≥1/1,000, <1/100
Rare: ≥1/10,000, <1/1,000
Very rare: <1/10,000 including isolated reports

Blood and lymphatic system disorders: *Rare*: lymphadenopathy

Metabolism and nutrition disorders: *Common*: appetite lost

Psychiatric disorders: *Very common*: irritability

Nervous system disorders: *Common*: headache (very common with 10 µg formulation), drowsiness; *Uncommon*: dizziness; *Rare*: paresthesia

Gastrointestinal disorders: *Common*: gastrointestinal symptoms (such as nausea, vomiting, diarrhea, abdominal pain)

Skin and subcutaneous tissue disorders: *Rare*: rash, pruritus, urticaria

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*: swelling at injection site, malaise, injection site reaction (such as induration), fever (≥37.5°C); *Uncommon*: influenza-like illness

Post-marketing Data

Infections and infestations: Meningitis

Blood and lymphatic system disorders: Thrombocytopenia

Immune system disorders: Anaphylaxis, allergic reactions including anaphylactoid reactions and mimicking serum sickness

Nervous system disorders: Paralysis, convulsions, hypoaesthesia, encephalitis, encephalopathy, neuropathy, neuritis

Vascular disorders: Hypotension, vasculitis

Skin and subcutaneous tissue disorders: Angioneurotic oedema, lichen planus, erythema multiforme

Musculoskeletal and connective tissue disorders: Arthritis, muscular weakness

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

ENGERIX-B induces specific humoral antibodies against the surface antigen of hepatitis B virus (anti-HBs antibodies). An anti-HBs antibody titre above 10 IU/l correlates with protection to HBV infection.

Pharmacodynamic effects

Protective efficacy

At risk groups:

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

A 95% protective efficacy was demonstrated in neonates of HBeAg positive mothers, immunised according to the 0, 1 and 2 or 0, 1 and 6 schedules without the concomitant administration of HBIg at birth. However, simultaneous administration of HBIg and vaccine at birth increased the protective efficacy to 98%.

Twenty years after primary vaccination during infancy, subjects born to mothers who were HBV carriers, received a challenge dose of ENGERIX-B. One month later, at least 93% of subjects (N=75) mounted an anamnestic response demonstrating immune memory.

Healthy subjects:

When the 0, 1 and 6 month schedule is followed, 96 % of vaccinees have seroprotective levels of antibody 7 months after the first dose.

When the 0, 1 and 2 month primary schedule plus a booster at month 12 is followed, 15 % and 89 % of vaccinees have seroprotective levels of antibody one month after first dose and one month after completion of the primary schedule respectively. One month after the booster dose 95.8 % of vaccinees achieved seroprotective levels of antibody.

For use in exceptional circumstances, the 0, 7 and 21 day primary schedule plus a booster at month 12 results in 65.2 % and 76% of vaccinees having seroprotective levels of antibody within 1 and 5 weeks respectively following completion of the primary schedule. One month after the booster dose 98.6 % of vaccinees achieved seroprotective levels of antibody.

The seroprotection rates (SP) obtained with a schedule of 0, 1, and 6 months in subjects from 11 years up to and including 15 years of age were evaluated up to 66 months after the first dose of the primary vaccination and are presented in the Table below:

Vaccine groups	Anti-HBs Month 2 SP (%)	Anti-HBs Month 6 SP (%)	Anti-HBs Month 7 SP (%)	Anti-HBs Month 30 SP (%)	Anti-HBs Month 42 SP (%)	Anti-HBs Month 54 SP (%)	Anti-HBs Month 66 SP (%)
ENGERIX-B 10 µg (0, 1, 6 months schedule)	55.8	87.6	98.2	96.9	92.5	94.7	91.4

These data show that a primary vaccination with ENGERIX-B vaccine induces circulating anti-HBs antibodies that persist for at least 66 months. All children (including subjects with anti-HBs antibody concentrations < 10 IU/l) received a challenge dose 72 to 78 months after primary vaccination. One month after the challenge dose, all children mounted an anamnestic response to the challenge dose and were shown to be seroprotected (i.e. anti-HBs antibody concentrations $\geq$ 10 IU/l). These data suggest that protection against hepatitis B may still be conferred through immune memory in all subjects who responded to primary vaccination but lost seroprotection level of anti-HBs antibodies.

Rechallenge in healthy subjects:

Healthy subjects (N=284) aged 12 to 13 years vaccinated during infancy with 3 doses of ENGERIX-B received a challenge dose of ENGERIX-B. One month later, 98.9% of subjects were shown to be seroprotected.

Patients with type II diabetes:

The seroprotection rates in subjects 20 years of age and above with type II diabetes were evaluated one month after the last dose of the primary vaccination and are presented in the Table below:

Age (years)	Schedule	Seroprotection rate at Month 7
20-39	0, 1, 6 months (20 µg)	88.5 %
40-49		81.2 %
50-59		83.2 %
≥ 60		58.2 %

Reduction in the incidence of hepatocellular carcinoma in children:

A significant reduction in the incidence of hepatocellular carcinoma has been observed in children aged 6-14 years following a nationwide hepatitis B vaccination in Taiwan. There was a significant decline in the prevalence of hepatitis B antigen, the persistence of which is an essential factor in the development of hepatocellular carcinoma.

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data

Appropriate safety tests have been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The final vaccines also contain aluminium hydroxide hydrate, sodium chloride, dibasic sodium phosphate dihydrate, monobasic sodium phosphate dihydrate, water for injections and traces of polysorbate 20.

6.2 Incompatibilities

ENGERIX-B should not be mixed with other vaccines.

6.3 Shelf life

The shelf-life of ENGERIX-B, 20 μg per 1.0 mL and 10 μg per 0.5 mL is 36 months from the date of manufacture when stored at +2°C to +8°C. The expiry date is shown on the labelling.

Accelerated stability tests at higher temperatures indicate that it will maintain full potency for over four years. ENGERIX-B has been kept at +37°C for seven days without any loss of its immunogenicity in man.

6.4 Special precautions for storage

The vaccine should be shipped under refrigeration and stored at +2°C to +8°C. Do not freeze, discard if the vaccine has been frozen.

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

Monodose presentations do not contain a preservative.

Upon storage, a fine white deposit with a clear colourless supernatant may be observed. The vaccine should be well shaken before use to obtain a slightly opaque, white suspension.

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.

6.5 Nature and contents of container

ENGERIX-B paediatric dose: 10 microgram (µg) dose vaccine

- 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.
- 0.5 mL of suspension in a vial (type I glass) with a stopper (butyl rubber).

Pack of one monodose vial.
Pack of one prefilled syringe.

ENGERIX-B: 20 microgram (µg) dose vaccine

- 1 mL of suspension in a pre-filled syringe (type I glass) with a plunger stopper (butyl rubber) and with a rubber tip cap.
- 1 mL of suspension in a vial (type I glass) with a stopper (butyl rubber).

Pack of one or three monodose vials.
Pack of one or 10 prefilled syringes.

The tip cap and rubber plunger stopper of the pre-filled syringe and the stopper of the vial are not made with natural rubber latex.

Not all pack sizes or presentations may be marketed.

6.6 Special precautions for disposal and other handling

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

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

GlaxoSmithKline NZ Limited
Private Bag 106600
Downtown
Auckland
NEW ZEALAND

ph (09) 367 2900
fax (09) 367 2910

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine: 24 March 1988

10. DATE OF REVISION OF THE TEXT

1 March 2023

Summary table of changes

Section changed	Summary of new information
4.2	Updates to instructions for use
6.5	Revision to container information

Version 10.0