EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 December 2024
EMA/CHMP/BPWP/143744/2011 rev.2
Committee for Medicinal Products for Human Use (CHMP)

Guideline on core SmPC for human normal immunoglobulin for subcutaneous and intramuscular administration (SCIg/IMIg)

Draft

Draft agreed by Haematology Working Party	25 October 2024
Adopted by CHMP for release for consultation	2 December 2024
Start of public consultation	5 December 2025
End of consultation (deadline for comments)	13 June 2025

This guideline replaces 'Guideline on core SPC for human normal immunoglobulin for subcutaneous and intramuscular administration' (EMA/CHMP/BPWP/143744/2011 rev.1).

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support.

Keywords	***SCIg, IMIg, human normal immunoglobulin, primary and secondary immunodeficiency syndromes, hepatitis A prophylaxis, immunomodulation, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).***

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Guideline on core SmPC for human normal immunoglobulin for subcutaneous and intramuscular administration (SCIg/IMIg)

Table of contents

Executive summary 3

1. Introduction (background) 3

2. Scope 3

3. Legal basis 4

4. References 4

SUMMARY OF PRODUCT CHARACTERISTICS 6

4.1 Therapeutic indications 7

4.2 Posology and method of administration 8

4.3 Contraindications 10

4.4 Special warnings and precautions for use 10

4.5 Interaction with other medicinal products and other forms of interaction 12

4.6 Fertility, pregnancy and lactation 12

4.7 Effects on ability to drive and use machines 12

4.8 Undesirable effects 12

4.9 Overdose 14

5.1 Pharmacodynamic properties 14

5.2 Pharmacokinetic properties 14

5.3 Preclinical safety data 14

6.1 List of excipients 15

6.2 Incompatibilities 15

6.3 Shelf life 15

6.4 Special precautions for storage 15

6.5 Nature and contents of container 15

6.6 Special precautions for disposal <and other handling> 15

Executive summary

This guideline describes the information to be included in the Summary of Product Characteristics (SmPC) for human normal immunoglobulins for subcutaneous and/or intramuscular administration (SCIg/IMIg).

1. Introduction (background)

The purpose of this core SmPC is to provide applicants and regulators with harmonised guidance on the information to be included in the Summary of product characteristics (SmPC) for a human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg). The choice of text will depend on whether the product is for both subcutaneous and intramuscular administration or only one of these routes. This guideline should be read in conjunction with the current version of the Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and intramuscular administration (EMA/CHMP/BPWP/410415/2011 rev 2).

The Quality Review of Documents (QRD) product information template with explanatory notes (QRD PI annotated template1) and the QRD convention to be followed for the EMA-QRD templates2 provide general guidance on format and text and should be read in conjunction with the core SmPC and the Guideline on summary of product characteristics3.

This core SmPC has been prepared based on SmPCs of authorised medicinal products and considering the published scientific literature. Any marketing authorisation application or variation of a marketing authorisation for a human normal immunoglobulin should be accompanied by the required data particulars, documents, literature and/or justification for the application to be valid.

For parenteral products such as SCIg and IMIg, practical information relevant for healthcare professionals, especially the posology and method of administration, should be included at the end of the package leaflet since the SmPC is not always readily available (see the QRD annotated template for further guidance on how to present such information).

In addition, for the content of sections 4.4 and 4.8 concerning transmissible agents, refer to the current version of the Guideline on the warning on transmissible agents in SmPCs and package leaflets for plasma-derived medicinal products (EMA/CHMP/BWP/360642/2010 current version4).

This revision (2024) includes updates to the guideline to be consistent where applicable with the revised Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg) (EMA/CHMP/BPWP/94038/2007 Rev. 6)5 and the inclusion of the indication for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

2. Scope

This core SmPC covers human normal immunoglobulin for subcutaneous and intramuscular administration (SCIg/IMIg) defined by the relevant European Pharmacopoeia monographs. It does not apply to products intentionally prepared to contain fragmented or chemically modified IgG.

[1] https://www.ema.europa.eu/en/documents/template-form/qrd-product-information-annotated-template-english-version-104-highlighted_en.pdf
[2] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/quality-review-documents-qrd-convention-be-followed-european-medicines-agency-qrd-templates_en.pdf
[3] https://health.ec.europa.eu/system/files/2016-11/smpc_guideline_rev2_en_0.pdf
[4] Guideline on transmissible agents in SmPC - plasma-d products 2010 (europa.eu)
[5] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-core-smpc-human-normal-immunoglobulin-intravenous-administration-ivig-rev-6_en.pdf

3. Legal basis

This guideline has to be read in conjunction with Article 11 of Directive 2001/83/EC as amended, and the introduction and general principles (4) and part I of the Annex I to Directive 2001/83/EC as amended.

4. References

European Academy of Neurology/Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint Task Force—Second revision Peter Y. K. Van den Bergh et al First published: 30 July 2021 https://doi.org/10.1111/ene.14959

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European consensus-based recommendations for the diagnosis and treatment of Kawasaki disease - the SHARE initiative Nienke de Graeff et al. Rheumatology 2019;58:672-682 doi:10.1093/rheumatology/key344

Kawasaki Disease: an Update Eileen Rife et al. Current Rheumatology Reports (2020) 22:75 https://doi.org/10.1007/s11926-020-00941-4

Effectiveness and Safety of an Intravenous Immune Globulin (IVIG) Preparation in Post-exposure Prophylaxis (PEP) Against Measles in Infants Benno Kohlmaier et al. Front. Pediatr. 9:762793. doi: 10.3389/fped.2021.762793

121 Clinical experience of intramuscular immunoglobulin for measles prophylaxis in children: Is it practical?
122 Leanne Philips et al. Journal of Paediatrics and Child Health 56 (2020) 364–366 doi:10.1111/jpc.14800

123 Fachliche Anwendungshinweise zur Masern-Postexpositionsprophylaxe bei Risikopersonen
124 Stellungnahme der Ständigen Impfkommission (STIKO) am RKI; Epidemiologisches Bulletin 12. Januar
125 2017 / Nr. 2

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

<▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.> [For medicinal products subject to additional monitoring ONLY]

1. NAME OF THE MEDICINAL PRODUCT

{(Invented) name strength pharmaceutical form}

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Human normal immunoglobulin (<SCIg> <and> <IMIg>)

[Product-specific information on quantitative composition. Include: IgG subclasses, human protein content and minimum content of IgG, maximum IgA content]

One ml contains:
Human normal immunoglobulin……..{X} mg
(purity of at least {XX}% IgG)

Each {container e.g. vial} of {xx} ml contains: {X} g of human normal immunoglobulin

<Antibodies to Hepatitis A at least {x} IU/ml>

Distribution of the IgG subclasses (approx. values):
IgG1 ..... {XX.X}%
IgG2 ..... {XX.X}%
IgG3 ..... {XX.X}%
IgG4 ..... {XX.X}%

The maximum IgA content is {x} micrograms/ml.

Produced from the plasma of human donors.

<u><Excipient(s) with known effect></u>

<For the full list of excipients, see section 6.1.>

3. PHARMACEUTICAL FORM

[Product specific, including osmolality]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[Age ranges given in this section may require modification if there are any safety issues for the excipients used for a particular product e.g. sorbitol risk for babies and young children with hereditary fructose intolerance.]

<u>Indications for subcutaneous administration (SCIg)</u>

Replacement therapy in adults, children and adolescents (0-18 years) in:

- Primary immunodeficiency syndromes (PID) with impaired antibody production (see section 4.4).
- Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure (PSAF)* or serum IgG level of <4g/l.

*PSAF = failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines.

Immunomodulation in adults, children and adolescents (0–18 years) in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) as maintenance therapy after stabilisation with IVIg.

<u><Indications for intramuscular administration (IMIg)</u>

[Product-specific for SC/IMIg with a minimum antibody content for HAV of 100 IU/ml:]

Hepatitis A prophylaxis

In adults and children and adolescents (0-18 years)

- Pre-exposure prophylaxis, preferably in combination with vaccination, in unvaccinated individuals travelling in less than 2 weeks to areas at risk of hepatitis A.
- Post-exposure prophylaxis in unvaccinated individuals within 2 weeks of hepatitis A virus (HAV) exposure.

For long-term hepatitis A prophylaxis, vaccination is recommended. >

<Consideration should also be given to other official guidance on the appropriate use in hepatitis A prophylaxis.>

[For product-specific immunomodulatory indications - see current version of the Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (EMA/CHMP/BPWP/410415/2011 rev 2). These product-specific indications should state in which age groups the product is indicated, specifying the age limits, e.g. 'X is indicated in <adults><neonates><infants><children> <adolescents> <aged x to y <years, months>>.]

4.2 Posology and method of administration

Replacement therapy should be initiated and monitored under the supervision of a physician experienced in the treatment of immune system disorders.

<u>Posology</u>

The dose and dose regimen are dependent on the indication.

Replacement therapy
The medicinal product should be administered via the subcutaneous route.

In replacement therapy, the dose may need to be individualised for each patient depending on the pharmacokinetic and clinical response.
<This medicinal product can be administered at regular intervals from once daily up to every other week.>
The following dose regimens are given as a guideline.

Replacement therapy in primary immunodeficiency syndromes (see section 4.1)
The dose regimen should achieve a trough level of IgG (measured before the next infusion) of at least 5 to

6 g/l and aim to be within the reference interval of serum IgG for age. A loading dose of at least 0.2 to 0.5 g/kg (1.2 to 3.0 ml/kg) body weight may be required. This may need to be divided over several days, with a maximal daily dose of 0.1 to 0.15 g/kg.

After steady state IgG levels have been attained, maintenance doses are administered at repeated intervals to reach a cumulative monthly dose of the order of 0.4-0.8 g/kg (2.4 to 4.8 ml/kg). Each single dose may need to be injected at different anatomic sites.
Trough levels should be measured and assessed in conjunction with the incidence of infection. To reduce the rate of infection, it may be necessary to increase the dose and aim for higher trough levels.

Replacement therapy in secondary immunodeficiencies (see section 4.1.)
The recommended dose administered at regular intervals (approximately once per week) is to reach a cumulative monthly dose of the order of 0.2-0.4 g/kg (1.2 – 2.4 ml/kg). Each single dose may need to be injected at different anatomic sites.
IgG trough levels should be measured and assessed in conjunction with the incidence of infection. The dose should be adjusted as necessary to achieve optimal protection against infections; an increased dose may be required in patients with persisting infection, and a decreased dose can be considered when the patient remains infection free.

<Hepatitis A prophylaxis
The product should be administered via the intramuscular route.

To achieve a minimum protective level of 10 mIU/ml with an IMIg with a minimum antibody content for HAV of 100 IU/ml, the following dose is recommended:

- Pre-exposure prophylaxis in unvaccinated individuals travelling in less than 2 weeks to areas of hepatitis A risk (short term prophylaxis):
For stays in endemic areas of less than 3 months: 0.17 ml/kg body weight (preferably given in combination with vaccination).

- Post-exposure prophylaxis in unvaccinated individuals within 2 weeks of exposure: 0.17 ml/kg body weight.>

Immunomodulatory therapy in CIDP
Treatment is initiated 1 week after the last IVIg infusion. The recommended subcutaneous dose is 0.2 to 0.4 g/kg body weight per week administered in 1 or 2 sessions over 1 or 2 consecutive days. The initial subcutaneous dose may be a 1:1 conversion from the previous IVIg dose (calculated as weekly dose).
Example: a 1 g/kg IVIg dose given every 3 weeks would convert into a 0.33 g/kg dose given once a week.
The weekly dose can be divided into smaller doses and administered by desired number of times per week.
For dosing every two weeks, the weekly dose should be doubled.

Elderly
No dose adjustment is required unless clinically warranted (see section 4.4).

Hepatic impairment
No evidence is available to require a dose adjustment.

Renal impairment
No dose adjustment is required unless clinically warranted (see section 4.4).

Paediatric population
The posology in children and adolescents (0-18 years) is not different to that of adults as the posology for each indication is given by body weight and adjusted to the clinical outcome of the above-mentioned conditions.

Method of administration

For subcutaneous use <only>.

Subcutaneous infusion for home treatment should be initiated and monitored by a physician experienced in the guidance of patients for home treatment. The patient must be instructed in the use of a syringe driver, the infusion techniques, the keeping of treatment diary, recognition of and measures to be taken in case of severe adverse reactions.

{(Invented) name} may be injected into sites such as abdomen, thigh, upper arm, and lateral hip.
It is recommended to use an initial administration speed of {XX} mL/kg/hr.
If well tolerated (see section 4.4), the infusion speed can be enhanced by {YY} mL/kg/hr every subsequent infusion. The recommended maximum speed is {ZZ} mL/kg/hr. More than one pump can be used simultaneously. The amount of product infused into a particular site varies. In infants and children, infusion site may be changed every 5-15 ml. In adults, doses over 30 ml may be divided according to patient preference. There is no limit to the number of infusion sites.

<For intramuscular use.>
<Intramuscular injection must be given by a physician or nurse.>

4.3 Contraindications

Hypersensitivity to the active substance (human immunoglobulin) or to any of the excipients (see sections 4.4 and 6.1). *[Product-specific contraindications].*
{(Invented) name} must not be given intravascularly.

It must also not be administered intramuscularly in case of severe thrombocytopenia and in other disorders of haemostasis.

4.4 Special warnings and precautions for use

[In addition to the text below, include any additional product-specific precautions for use and warnings (e.g. those relating to excipients present in the product).]

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

If {(Invented) name} is accidentally administered into a blood vessel, patients could develop shock.
The recommended infusion rate must be closely followed (see section 4.2). Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period.

Certain adverse reactions may occur more frequently in patients who receive human normal immunoglobulin for the first time or, in rare cases, when the human normal immunoglobulin product is switched or when there has been a long interval since the previous infusion.

Potential complications can often be avoided by ensuring that patients:

- are not sensitive to human normal immunoglobulins by initially injecting the product slowly (see section 4.2);
- are carefully monitored for any symptoms throughout the infusion period. In particular, patients naïve to human normal immunoglobulin, patients switched from an alternative immunoglobulin

product or when there has been a long interval since the previous infusion should be monitored during the first infusion and for the first hour after the first infusion in a controlled healthcare setting in order to detect potential adverse signs and to ensure that emergency treatment can be administered immediately should problems occur.
All other patients should be observed for at least 20 minutes after administration.

In case of adverse reaction, either the infusion rate must be reduced or the infusion stopped. The treatment required depends on the nature and severity of the adverse reaction.

Hypersensitivity

Hypersensitivity reactions are rare. They can particularly occur in patients with anti-IgA antibodies who should be treated with particular caution. Patients with anti-IgA antibodies, in whom treatment with subcutaneous IgG products remains the only option, should be treated with {(Invented) name} only under close medical supervision.
Rarely, human normal immunoglobulin can induce a fall in blood pressure with anaphylactic reaction, even in patients who had tolerated previous treatment with human normal immunoglobulin.
In case of shock, standard medical treatment for shock should be implemented.

Thromboembolism

Arterial and venous thromboembolic events including myocardial infarction, cerebral vascular accident (including stroke), deep vein thrombosis and pulmonary embolism have been associated with the use of immunoglobulins. Patients should be sufficiently hydrated before use of immunoglobulins. Caution should be exercised in patients with preexisting risk factors for thrombotic events (such as advanced age, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, patients with prolonged periods of immobilisation, severely hypovolemic patients, patients with diseases which increase blood viscosity).

Patients should be informed about first symptoms of thromboembolic events including shortness of breath, pain and swelling of a limb, focal neurological deficits and chest pain and should be advised to contact their physician immediately upon onset of symptoms.

[*For SCIg products, include the following warning:*]

<Aseptic meningitis syndrome (AMS)

Aseptic meningitis syndrome has been reported to occur in association with subcutaneous immunoglobulin treatment; the symptoms usually begin within several hours to 2 days following treatment. Discontinuation of immunoglobulin treatment may result in remission of AMS within several days without sequelae.
Patients should be informed about first symptoms which encompass severe headache, neck stiffness, drowsiness, fever, photophobia, nausea, and vomiting.>

Interference with serological testing

After injection of immunoglobulin the transitory rise of the various passively transferred antibodies in the patient's blood may result in misleading positive results in serological testing.
Passive transmission of antibodies to erythrocyte antigens, e.g. A, B, D may interfere with some serological tests for red cell antibodies for example the direct antiglobulin test (DAT, direct Coombs' test).

Transmissible agents

[The text to be inserted here for transmissible agents should be in accordance with the current version of the guideline on the Warning on Transmissible Agents in SmPCs and Package Leaflets for plasma-derived medicinal products (EMA/CHMP/BWP/360642/2010) rev. 1.]

Paediatric population

[Product specific]
<The listed warnings and precautions apply both to adults and children.>

4.5 Interaction with other medicinal products and other forms of interaction

Live-attenuated virus vaccines

Immunoglobulin administration may impair for a period of at least 6 weeks and up to 3 months the efficacy of live attenuated virus vaccines such as measles, rubella, mumps and varicella. After administration of this medicinal product, an interval of 3 months should elapse before vaccination with live-attenuated virus vaccines. In the case of measles, this impairment may persist for up to 1 year. Therefore patients receiving measles vaccine should have their antibody status checked.

Paediatric population

[Product specific]
<The listed interactions apply both to adults and children.>

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of this medicinal product for use in human pregnancy has not been established in controlled clinical trials. Therefore, this product should only be given with caution to pregnant women. Immunoglobulin products have been shown to cross the placenta, increasingly during the third trimester. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are to be expected.

Breast-feeding

The safety of this medicinal product for use during lactation has not been established in controlled clinical trials. Therefore, this product should only be given with caution during breast-feeding.
Immunoglobulins are excreted into human milk.
No adverse effects on the breastfed newborn/infant are anticipated.

Fertility

Clinical experience with immunoglobulins suggests that no harmful effects on fertility are to be expected.

[Any relevant product-specific information should be added.]

4.7 Effects on ability to drive and use machines

The ability to drive and operate machines may be impaired by some adverse reactions associated with {(Invented) name}. Patients who experience adverse reactions during treatment should wait for these to resolve before driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

[Frequencies of adverse reactions cited in the summary of safety profile should be stated as accurately as possible; please include incidence in brackets, if available.]

Adverse reactions such as chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain may occur occasionally.

Rarely human normal immunoglobulins may cause a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration.

Local reactions at infusion sites, such as swelling, soreness, redness, induration, local heat, itching, bruising and rash, may frequently occur.

For safety information with respect to transmissible agents, see section 4.4.

Tabulated list of adverse reactions

Adverse reactions from <clinical trials><post-authorisation safety studies><spontaneous reporting> are listed by MedDRA system organ classification (SOC and Preferred Term Level) in the table below.

Frequencies have been evaluated according to the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); very rare (<1/10 000), not known (cannot be estimated from the available data).

<Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.>

MeDRA System Organ Class (SOC)	**Adverse reaction**	**Frequency per patient**	**Frequency per infusion**
		<Very common> <common> <uncommon> <rare> <very rare><unknown>	<Very common> <common> <uncommon> <rare> <very rare><unknown>

Description of selected adverse reactions

[Product specific. If the safety profile is different depending on the route of administration, the differences should be mentioned here.]

Paediatric population

[Product specific]
<Frequency, type and severity of adverse reactions in children are <expected to be> the same as in adults.>

<Other special population(s)>

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 the national reporting system listed in Appendix V.

4.9 Overdose

<Consequences of an overdose are not known.>

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immune sera and immunoglobulins, immunoglobulins, normal human, ATC code: J06BA01

Human normal immunoglobulin contains mainly immunoglobulin G (IgG) with a broad spectrum of antibodies against infectious agents.
Human normal immunoglobulin contains the IgG antibodies present in the normal population. It is usually prepared from pooled plasma from not fewer than 1000 donations. It has a distribution of immunoglobulin G subclasses closely proportional to that in native human plasma. Adequate doses of this medicinal product may restore abnormally low immunoglobulin G levels to the normal range.

[Product specific for products with immunomodulatory indications:]
<The mechanism of action in indications other than replacement therapy is not fully elucidated, but includes immunomodulatory effects.>

[Product specific: Clinical study results can be briefly summarised here]

Paediatric population

[Product specific: The text should be in line with the Paediatric Regulation and the SmPC guideline. In case of a full waiver or any deferral, include the standard statement in accordance with the SmPC guideline.]

5.2 Pharmacokinetic properties

Following subcutaneous administration of {(Invented) name}, peak serum levels are achieved after approximately {X} days.

In a clinical trial with {(Invented) name} (n = {XX}), the subjects achieved sustained trough levels (median {XX} g/l) over a period of {YY} weeks when receiving median weekly doses of {ZZ} g/kg.

Absorption and distribution

[Product specific]

Elimination

IgG and IgG-complexes are broken down in cells of the reticuloendothelial system. *[Product specific]*

Paediatric population

[Product specific]

5.3 Preclinical safety data

[Product specific]

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[Product specific. Where applicable, the amount of albumin added as a stabiliser should be stated (Ph. Eur. labelling requirement).]

6.2 Incompatibilities

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

6.3 Shelf life

[Product specific: reference should be made to the SmPC guideline for stability at different temporary storage conditions.]

6.4 Special precautions for storage

[Product specific]

6.5 Nature and contents of container

[Product specific]

6.6 Special precautions for disposal <and other handling>

[Product specific]

The medicinal product should be brought to room or body temperature before use.
<Total reconstitution should be obtained within *[product-specific time]*.>
<Products should be inspected visually for particulate matter and discoloration prior to administration.>
The solution should be clear or slightly opalescent and colourless or pale yellow. Solutions that are cloudy or have deposits should not be used.

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

7. MARKETING AUTHORISATION HOLDER

[Product specific]

8. MARKETING AUTHORISATION NUMBER(S)

[Product specific]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[Product specific]

10. DATE OF REVISION OF THE TEXT

[Product specific]

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu<, and on the website of {name of MS Agency (link)}>.