SNIF: GMOB-2023-17153

Domain:
GMO

Authorisation type:
Deliberate release of GMO or a combination of GMOs for any other purpose than for placing on the market

Application type:
Summary notification for the release of genetically modified higher organisms other than higher plants in line with Decision 2002/813/EC Annex, Part 1.

Recipient Member State:
Portugal

Competent Authority:
Portuguese Environment Agency

Notification number:
B/PT/23/02

Acknowledgement date:
2023-03-06

A- General information

Details of notification

Details of notification
Deliberate release of GMO Axicabtagene Ciloleucel - SNIF
Member State of notification
Portugal
Title of the project
An Adaptive Phase 3, Randomized, Open-Label, Multicenter Study to Compare the Efficacy and Safety of Axicabtagene Ciloleucel versus Standard of Care Therapy as First-Line Therapy in Subjects with High-Risk Large B-Cell Lymphoma (ZUMA-23)
Proposed period of release
Starting date
2023-09-01
Finishing date
2031-03-31

Notifier

Name of institute or company
PPD Global Ltd Sucursal em Portugal
Email
maria.monteiro@ppd.com
Phone number
+351308806197
Website
Not provided
Address
Avenida da Liberdade 180 A - 4 Dto
Post code
1250-146 Lisbon
Country
Portugal

GMO characterisation

(a) Indicate whether the GMO is a:

Viroid
No
RNA virus
No
DNA virus
No
Bacterium
No
Fungus

No
Animal
Yes

Select from following options:

Mammal
Yes
Insect
No
Fish
No
Other animal
No
Other
No

(b) Identity of the GMO (genus and species)

KTE-C19 (axicabtagene ciloleucel) comprises of autologous human T cells transduced with a replication-incompetent retroviral vector encoding an anti-CD19 chimeric antigen receptor.

(c) Genetic stability - according to Annex IIIa, II, A(10)

Yes

Is the same GMO release planned elsewhere in the Community (in conformity with Article 6(1)), by the same notifier?

Yes
Country
Denmark
France
Italy
Netherlands
Estonia
Austria

Has the same GMO been notified for release elsewhere in the Community by the same notifier?

Yes
Member State of notification
SE
Insert the notification number(s) (if exist)
B/SE/18/2017-002261-22; B/SE/2015-005010-30
Member State of notification
FR
Insert the notification number(s) (if exist)
10953953; 9159321
Member State of notification

ES
Insert the notification number(s) (if exist)
B/ES/18/01
Member State of notification
DE
Insert the notification number(s) (if exist)
B/DE/17/PEI2927; B/DE/17/PEI3320

Has the same GMO been notified for release or placing on the market outside the Community by the same or other notifier?

Yes
Country
AU
Insert the notification number(s) (if exist)
N/A
Country
IL
Insert the notification number(s) (if exist)
N/A
Country
US
Insert the notification number(s) (if exist)
N/A
Country
CA
Insert the notification number(s) (if exist)
NSN-19821
Country
BR
Insert the notification number(s) (if exist)
SEI 01245.008746/2022-75; SEI 01245.008748/2022-64
Country
CH
Insert the notification number(s) (if exist)
N/A

Summary of the potential environmental impact of the release of the GMOs.

Environmental impact is not expected as the release of the transduced autologous T cells is limited to patient administration in hospital settings. According to the environmental risk assessment, KTE-C19 will not reach the environment at large. The overall risk of the GMO KTE-C19 and the PG13-CD19-H3 retroviral vector for people and the environment can be concluded to be negligible.

B. Information relating to the recipient or parental organisms from which the GMO is derived

1. Recipient or parental organism characterisation

Indicate whether the recipient or parental organism is a:

Viroid
No
RNA virus
No
DNA virus
No
Bacterium
No
Fungus
No
Animal
Yes

Select from following options:

Mammal
Yes
Insect
No
Fish
No
Other animal
No
Other
No

2. Name

(i) Order and/or higher taxon (for animals)
Homo sapiens
(ii) Genus

(iii) Species

(iv) Subspecies

(v) Strain

(vi) Pathovar (biotype, ecotype, race, etc.)

3. Geographical distribution of the organism

(a) Indigenous to, or otherwise established in, the country where the notification is made:
yes
(b) Indigenous to, or otherwise established in, other EC countries:
yes
Indicate the type of ecosystem in which it is found:
mediterranean
atlantic
boreal
macaronesian
alpine
continental
(c) Is it frequently used in the country where the notification is made?
Yes
(d) Is it frequently kept in the country where the notification is made?
Yes

4. Natural habitat of the organism

(a) Is the organism a microorganism ?
Yes
Water
No
Soil, free-living
No
Soil in association with plant-root systems
No
In association with plant leaf/stem systems
No
In association with animals
No
Other
Yes
Specify

(b) Is the organism an animal?
Yes
Natural habitat or usual agroecosystem
Human

5(a) Detection Techniques

Detection Techniques
Common techniques of blood cell analysis

5(b) Identification Techniques

Identification Techniques
Common techniques of blood cell analysis

6. Is the recipient organism classifies under existing Community rules relating to the protection of human health and/or the environment?

No

7. Is the recipient organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?

yes

To which of the following organisms

humans
No
animals
No
plants
No
Other
Yes
Give the relevant information specified under Annex III A, point II, (A)(11)(d) of Directive 2001/18/EC
Prior to apheresis, the patient's serum or plasma is tested in accordance with the requirements described in Commission Directive 2006/17/EC. Each patient is tested for the transmissible agents HIV-1/2, HBV, HCV, and syphilis screen. As stated in the study protocol, HIV+ patients with undetectable viral load can be enrolled in the study.

8. Information concerning reproduction

(a) Generation time in natural ecosystems:
N/A
(b) Generation time in the ecosystem where the release will take place:
N/A
(c) Way of reproduction
Asexual
(d) Factors affecting reproduction:

9. Survivability

(a) Ability to form structures enhancing survival or dormancy:

(i) endospores
No
(ii) cysts
No
(iii) sclerotia
No
(iv) asexual spores (fungi)
No
(v) sexual spores (fungi)
No
(vi) eggs
No
(vii) pupae
No

(viii) larvae
No
Other
Yes
Specify
Not applicable for human T cells
(b) Relevant factors affecting survivability
The survival of human T cells requires a complex combination of special media, temperature and CO2. The environmental conditions outside the host (body) are substantially different and will not support the cells survival (temperature, pH, UV and a change in the biophysical and biochemical conditions).

10(a) Ways of dissemination

Human T cells can only be transmitted between individuals through injection. No dissemination in the environment is anticipated due to fast inactivation and lack of a natural entry route into the body.
10(b) Factors affecting dissemination
The immune system of people other than the donor will eliminate the T cell product (the patient-specific genetically modified T cells).

11. Previous genetic modifications of the recipient or parental organism already notified for release in the country where the notification is made (give notification numbers)

N/A

C. Information relating to the genetic modification

1. Type of the genetic modification

Insertion of genetic material
Yes
Deletion of genetic material
No
Base substitution
No
Cell fusion
No
Other
No

2. Intended outcome of the genetic modification

KTE-C19 is a gene therapy whereby autologous T cells are genetically modified to express an anti-CD19 transmembrane Chimeric Antigen Receptor (CAR) that targets CD19 on the cell surface of malignant B cells. The CAR-modified T cell is activated following engagement with the CD19 target, resulting in elimination of the CD19 malignant cell.

3(a) Has a vector been used in the process of modification?

Yes
3(b) If yes, is the vector wholly or partially present in the modified organism?
Yes

4. If the answer to 3(b) is yes, supply the following information

(a) Type of vector

Plasmid
No
Bacteriophage
No
Virus
Yes
Cosmid
No
Transposable element
No
Other
No
(b) Identity of the vector
Replication-deficient gamma-retroviral vector: murine stem cell virus-based splice-gag vector (MSGV1) termed PG13-CD19-H3 Vector.
(c) Host range of the vector
The vector used is a hybrid retroviral vector consisting of the gag-pol accessory proteins from the Moloney murine leukemia virus (MoMLV) and the envelope from the gibbon ape leukemia virus (GALV), both

contained and produced in the mouse cell line PG13. The backbone containing the transgene is MSGV1, which utilizes the long terminal repeats (LTR) from the murine stem cell virus (MSCV) and an extended gag region and splice site to improve retroviral titer and expression of the transgene across different cell types {Hughes 2005}. This backbone is compatible with the MoMLV retroviral accessory proteins. The PG13-CD19-H3 Vector produced in the PG13 cell line has a broad host range including rat, hamster, bovine, cat, dog, monkey and human cells {Miller 1991}

(d) Presence in the vector of sequences giving a selectable or identifiable phenotype

Yes

Antibiotic resistance

No

Other

Yes

Specify

The vector encodes the anti-CD19 CAR which is expressed at the membrane surface of transduced T cells. Cell surface expression of the CAR can be detected by flow cytometric analysis of the transduced T cells, thereby providing an identifiable phenotype.

(e) Constituent fragments of the vector

The backbone containing the CAR sequence is MSGV1, which utilizes the long terminal repeats (LTR) from the MSCV and an extended gag region and splice site to improve retroviral titer and expression of the transgene across different cell types {Hughes 2005}. Only the LTRs and the sequences contained in between are integrated in the genome of the transduced T cells as provirus. This provirus therefore contains a 5LTR serving as promoter, a partial gag sequence and packaging signal, a CAR sequence and a 3LTR.

(f) Method for introducing the vector into the recipient organism

(i) transformation

No

(ii) electroporation

No

(iii) macroinjection

No

(iv) microinjection

No

(v) infection

No

Other

Yes

Specify

Transduction

6. Composition of the insert

(a) Composition of the insert

The PG13-CD19-H3 Vector encodes the anti-CD19 CAR. The process of retroviral mediated transduction serves to integrate the CAR gene into the T cell genome. The transfer plasmid MSGV1-FMC63-CD28z is an engineered construct that was used to generate an expression cell line that constitutively produces the PG13-CD19-H3 Vector. It comprises 5 and 3 LTRs flanking a partial gag sequence, a retroviral packaging signal and the DNA sequence encoding the anti-CD19 CAR. The anti-CD19 CAR constituent consists of the following domains linked as a single chimeric molecule: A target-specific binding domain consisting of an

antibody-derived single-chain variable fragment (scFv) specific for the target antigen CD19 expressed on the surface of normal and malignant B cells; the human T cell-derived activating domains CD3-zeta and CD28; and the transmembrane and hinge domains of human CD28.

(b) Source of each constituent part of the insert

The CAR construct utilised to produce KTE-C19 has been designed, optimised and initially tested at the Surgery Branch of the NCI {Kochenderfer 2009, Kochenderfer 2010}. The scFv fragment was derived from the variable region of the anti-CD19 monoclonal antibody FMC63 which is murine in origin. {Nicholson 1997}. The remainder of the CAR sequences, namely the hinge and transmembrane domains, CD3-zeta and CD28 signaling domains, are all of human origin, having been cloned from human T cells. The signalling domain of the CD3-zeta chain is of human origin and is essential for mediating T cell activation. The cytoplasmic domain of the CD28 costimulatory molecule is also included, since murine models and clinical studies have demonstrated the importance of CD28- mediated costimulation for optimal survival, persistence and anti-tumour activity of anti CD19 CAR T cells {Kowolik 2006}. The CD3-zeta chain and CD28 fragments were cloned from human T cells into a contiguous chimeric single chain construct and inserted in the MSGV1 plasmid.

(c) Intended function each constituent part of the insert in the GMO

Please refer to 6.a. (Composition of the insert) and 6.b. (Source of each constituent part of the insert). As per 4.e. (Constituent fragments of the vector) the retroviral integrase mediates the insertion of the retro-transcribed viral genome into the host genome via its interaction with the two LTRs, resulting in the integration of both LTRs along with all the nucleotide sequences found in between them, including the CAR. One of the LTRs serves as the promoter once the DNA is fully incorporated in the host genome, driving the expression of the CAR. Target Binding Domain: At one end of the CAR is a target binding domain of an antibody that is specific for the target antigen CD19 present on the surface of normal and malignant B cells. This domain extends out of the engineered T cell into the extracellular space, where it can recognise target antigens. The target binding domain consists of a single-chain variable fragment, or scFv, derived from an antibody comprising variable domains of heavy and light chains joined by a short linker. This allows the expression of the CAR as a single-chain protein. Transmembrane Domain and Hinge: This middle portion of the CAR links the scFv target binding domain to the activating elements inside the cell. This transmembrane domain anchors the CAR in the cells membrane. In addition, the transmembrane domain may also interact with other transmembrane proteins that enhance CAR function. In the extracellular region of the CAR, directly adjacent to the transmembrane domain, lies a hinge domain. This region of the CAR provides structural flexibility to facilitate optimal binding of the CARs scFv target binding domain with the target antigen on the cancer cells surface. Activating Domains: Located within the T cells interior are two regions of the CAR responsible for activating the T cell upon binding to the target cell. The CD3-zeta element delivers essential primary signal within the T cell, and the CD28 element delivers an additional, co-stimulatory signal that promotes T cell survival, persistence and anti-tumour activity. Together, these signals trigger T cell activation, resulting in CAR T cell proliferation and direct killing of CD19-expressing normal and malignant cells. In addition, T cell activation stimulates the local secretion of cytokines and other molecules that can recruit and activate additional anti-tumour immune cells.

(d) Location of the insert in the host organism

On a free plasmid
No
Integrated in the chromosome
Yes
Other
No

(e) Does the insert contain parts whose product or function are not known?

No

D. Information on the organism(s) from which the insert is derived

1. Indicate whether it is a:

Viroid
No
RNA virus
Yes
DNA virus
No
Bacterium
No
Fungus
No
Animal
Yes

Select from following options:

Mammal
Yes
Insect
No
Fish
No
Other animal
No
Other
No

2. Complete name

(i) Order and/or higher taxon (for animals)
Orthoretrovirinae; (subfamily Oncovirinae)
(ii) Family name (for plants)

(iii) Genus
Gammaretrovirus
(iv) Species
Murine stem cell virus
(v) Subspecies
Oncovirinae type C (subfamily)
(vi) Strain

(vii) Cultivar/Breeding line

(viii) Pathovar

(ix) Common name
Gammaretrovirus

3. Is the organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?

no

(b) are the donated sequences involved in any way to the pathogenic or harmful properties of the organism?

no

Give the relevant information specified under Annex III A, point II, (A)(11)(d) of Directive 2001/18/EC

4. Is the donor organism classified under existing Community rules relating to the protection of human health and the environment, such as Directive 90/679/EEC on the protection of workers from risks related to exposure to biological agents at work?

No

5. Do the donor and recipient organism exchange genetic material naturally?

no

E. Information relating to the genetically modified organism

1. Genetic traits and phenotypic characteristics of the recipient or parental organism which have been changed as a result of the genetic modification

(a) Is the GMO different from the recipient as far as survivability is concerned?
no
Specify
(b) Is the GMO in any way different from the recipient as far as mode and/or rate of reproduction is concerned?
no
Specify
(c) Is the GMO in any way different from the recipient as far as dissemination is concerned?
no
Specify
(d) Is the GMO in any way different from the recipient as far as pathogenicity is concerned?
no
Specify

2. Genetic stability of the genetically modified organism

The CAR is introduced in the T cells via retroviral vector gene transfer. After integration, the gene modified autologous T cells are genetically stable.

3. Is the GMO significantly pathogenic or harmfull in any way (including its extracellular products), either living or dead?

no
(b) Give the relevant information under Annex III A, point II (A)(11)(d) and II(C)(2)(i):
The replication-deficient retroviral vector genome is integrated as a provirus in the T cell genome. No new viral particles can be assembled in the final host cell due to the absence in this proviral form of all the accessory proteins that confer infectivity and replicative potential to the retrovirus. In addition, the transgene inserted in the retroviral vector does not code for pathogenicity factors, cytokine-coding sequences, oncogenes, antibiotic resistance genes, or other hazardous inserts.

4. Description of identification and detection methods

(a) Techniques used to detect the GMO in the environment
CAR expression on transduced T cells can be detected using flow cytometry.
(b) Techniques used to identify the GMO
The GMO can be identified using flow cytometry. Integrated copies of the retroviral vector can be identified in T cells by qPCR.

F. Information relating to the release

1. Purpose of the release (including any significant potential environmental benefits that may be expected)

The purpose of the release is the treatment of adult patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL), high-grade B-cell lymphoma (HGBL), primary mediastinal B-cell lymphoma (PMBCL), and follicular lymphoma (FL).

2. Is the site of the release different from the natural habitat or from the ecosystem in which the recipient or parental organism is regularly used, kept or found?

No

3. Information concerning the release and the surrounding area

(a) Geographical location (administrative region and where appropriate grid reference):

KTE-C19 will only be supplied to hospitals and associated centres that are qualified in accordance with the agreed control distribution program.

(b) Size of the site (m2)

(i) actual release site (m2)

(ii) wider release area (m2)

(c) Proximity to internationally recognised biotopes or protected areas (including drinking water reservoirs), which could be affected:

N/A

(d) Flora and fauna including crops, livestock and migratory species which may potentially interact with the GMO

N/A

4. Method and amount of release

(a) Quantities of GMOs to be released:

Each single infusion bag of KTE-C19 contains a suspension of anti-CD19 CAR-T cells in approximately 68 mL for a target dose of 2.0 x 106 anti-CD19 CAR T cells/kg body weight. KTE-C19 may be administered to a patient.

(b) Duration of the operation:

The complete administration procedure including preparation of the infusion system is expected to take less than 24 hours.

(c) Methods and procedures to avoid and/or minimise the spread of the GMOs beyond the site of the release

Treatment with KTE-C19 will be carried out at hospital centres by experienced healthcare professionals who have been trained in handling live human cells and sufficiently aware of local institutional practices and policies related to hygiene and standards for safety and infectious materials handling. Healthcare professionals will receive educational materials in order to be familiar with the product characteristics of KTE-C19. The adequate training of personnel for general biosafety measures as well as the establishment and maintenance of training records on this item is the responsibility of the hospital centres as for all standard biosafety procedures. Kite will supply appropriate information to the responsible clinician, on the safe handling and storage.

5. Short description of average environmental conditions (weather, temperature etc.)

Hospital treatment rooms have to fulfil hygiene conditions required for the treatment of immune-compromised patients.

6. Relevant data regarding previous releases carried out with the same GMO, if any, specially related to the potential environmental and human health impacts from the release

N/A

G. Interactions of the GMO with the environment and potential impact on the environment, if significantly different from the recipient or parent organism

1. Name of target organisms (if applicable)

Applicable?
Yes
(i) Order and/or higher taxon (for animals)
Human
(ii) Family name (for plants)

(iii) Genus

(iv) Species

(v) Subspecies

(vi) Strain

(vii) Cultivar/Breeding line

(viii) Pathovar

(ix) Common name

2. Anticipated mechanism and result of interaction between the released GMOs and the target organism (if applicable)

Applicable?
Yes
Specify
The purpose of administering KTE-C19 finished product is for the treatment of Relapsed/Refractory (r/r) refractory diffuse large B-cell lymphoma (DLBCL), high-grade B-cell lymphoma (HGBL), primary mediastinal B-cell lymphoma (PMBCL), and follicular lymphoma (FL). KTE-C19, a CD19 directed autologous CAR-T cell therapy, binds to CD19 expressing cancer cells and normal B cells. Studies demonstrated that following anti CD19 CAR-T cell engagement with CD19 expressing target cells, the CD28 co-stimulatory domain and CD3 zeta signalling domain activate downstream signalling cascades that lead to T cell activation, proliferation, acquisition of effector functions and secretion of inflammatory cytokines and chemokines. This sequence of events leads to killing of CD19 expressing cells.

3. Any other potentially significant interactions with other organisms in the environment

None expected.

4. Is post-release selection such as increased competitiveness, increased invasiveness for the GMO likely to occur?

no

5. Types of ecosystems to which the GMO could be disseminated from the site of release and in which it could become established

The predicted habitat of KTE-C19 is humans. Human cells cannot proliferate in the environment as they can only survive inside the human body or under in vitro culture conditions. The patients own T cells are not shed from the patient after administration of KTE-C19.

6. Complete name of non-target organisms which (taking into account the nature of the receiving environment) may be unintentionally significantly harmed by the release of the GMO

(i) Order and/or higher taxon (for animals)
Not Applicable
(ii) Family name (for plants)

(iii) Genus

(iv) Species

(v) Subspecies

(vi) Strain

(vii) Cultivar/Breeding line

(viii) Pathovar

(ix) Common name

7. Likelihood of genetic exchange in vivo

(a) from the GO to other organisms in the release ecosystem:
For trials including HIV positive patients, please note that as the commercial license allows treatment of HIV positive patients at the discretion of the physician, the Sponsor considers that the environmental risk assessment of the marketing authorisation already adequately covers the overall risk of axicabtagene ciloleucel used in the current clinical trial. There is no additional risk minimisation measure(s) warranted. The clinical trial has the same level of risk posed by the use of the marketed product Yescarta, and this risk is considered to be negligible for both.
(b) from other organisms to the GMO:
None
(c) likely consequences of gene transfer**
N/A

8. Give references to relevant results (if available) from studies of the behaviour and characteristics of the GMO and its ecological impact carried out in simulated natural environments (e.g. microcosms etc.):

N/A

9. Possible environmentally significant interactions with biogeochemical processes (if different from the recipient or parental organism)

None

H. Information relating to monitoring

H. Information relating to monitoring

1. Methods for monitoring the GMOs
Patients should be monitored daily for the first 10 days following infusion for signs and symptoms of potential CRS, neurologic adverse reactions/immune effector cell-associated neurotoxicity syndrome (ICANS) and other toxicities. After the first 10 days following the infusion, the patient should be monitored at the physicians discretion. Patients should be instructed to remain within proximity of a qualified clinical facility for at least 4 weeks following infusion. Post-marketing monitoring of KTE-C19 will be carried out in the context of the routine pharmacovigilance program and the KTE-C19 risk management plan. The use of KTE-C19 is restricted to intravenous application to a relatively limited number of patients. Given the controlled, contained use-like conditions under which the administration of the product occurs, no intended deliberate release of this product into the environment is expected to take place. The overall risk of KTE-C19 for the environment is concluded to be negligible. Therefore, an environmental monitoring plan in accordance with Council Decision 2002/811/EC, is not provided.
2. Methods for monitoring ecosystem effects
N/A
3. Methods for detecting transfer of the donated genetic material from the GMO to other organisms
N/A
4. Size of the monitoring area (m2)
N/A
5. Duration of the monitoring
Refer to response provided in H.1.
6. Frequency of the monitoring
Refer to response provided in H.1.

I. Information on post release and waste treatment

I. Information on post release and waste treatment

1. Post-release treatment of the site
All non-disposable equipment will be cleaned per local biosafety guidelines. The patients room will be cleaned and disinfected according to routine cleaning and disinfection procedures for instance a hydrogen peroxide solution or any other method indicated for disinfection.
2. Post-release treatment of the GMOs
None
3(a) Type and amount of waste generated
Empty bags and the used delivery system components (e.g., guide tube, cannula, injection needles and syringes), gauzes, personal protective equipment (e.g. gloves etc) and components used for collecting body fluids samples after administration.
3(b) Treatment of waste
As this medicine will be administered by qualified healthcare professionals, they are responsible for ensuring the disposal of unused product and all material that has been in contact with KTE-C19 (solid and liquid waste) which should be disposed of as potentially infectious waste in accordance with local biosafety guidelines. Once KTE-C19 is administered to the patient, empty bags and the used delivery system components or any other components that have been in contact with the product before and during administration will be disposed of per local biosafety guidelines according to standard hospital procedures. These do not contain viral particles and any genetically modified cells present in the samples do not represent a specific safety concern. A patients modified T cells are not shed via saliva, urine or faeces into the environment, including wastewater, and therefore no additional precautions are mandated.

J. Information on emergency response plans

J. Information on emergency response plans

1. Methods and procedures for controlling the dissemination of the GMO(s) in case of unexpected spread

There is negligible risk of environmental health hazard in the event of accident such as spillages. Healthcare professionals are instructed to take appropriate precautions (wearing gloves and glasses) when handling KTE-C19 to avoid potential transmission of infectious diseases. Both T cells and any potential residual retroviral vector particles within KTE-C19 are susceptible to common methods of inactivation applied to microbial agents, and to many virucidal disinfectants, including 1% sodium hypochlorite, 2% glutaraldehyde, formaldehyde and ethanol. Heat (>50C for 1 minute), UV radiation and low and high pH are also virucidal. KTE-C19 will be rapidly destroyed by standard means of disinfection or household cleaning solutions (e.g., bleach, soap, alcohol containing cleaning solutions). In case of spillage, local biosafety guidelines for cleaning and disinfection will be followed.

2. Methods for removal of the GMOs of the areas potentially affected

Per local biosafety guidelines according to standard hospital procedures.

3. Methods for disposal or sanitation of plants, animals, soils etc. that could be exposed during or after the spread

N/A

4. Plans for protecting human health and the enironment in the event of an undesirable effect

As this medicine will be given by qualified healthcare professionals, they are responsible for the correct disposal of the product if not administered to the patient. These measures will help protect the environment. Local biosafety guidelines should be followed for unused medicine or waste material. Reporting suspected adverse reactions after authorisation of the medicinal product 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.