**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Episalvan gel

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g gel contains: 100 mg extract (as dry extract, refined) from birch bark from *Betula pendula* Roth, *Betula pubescens* Ehrh. as well as hybrids of both species (equivalent to 0.5-1.0 g birch bark), corresponding to 72-88 mg betulin.

Extraction solvent: n-Heptane

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Gel.
Colourless to slightly yellowish, opalescent.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Treatment of partial thickness wounds in adults. See section 4.4 and 5.1 with respect to type of wounds studied.

### 4.2 Posology and method of administration

Posology

The gel should be applied to the wound surface at a thickness of approximately 1 mm and covered by sterile wound dressing. The gel should be re-applied at each wound dressing change, until the wound is healed, for up to 4 weeks (see section 4.4 “wound size” and “duration of use”).

Special populations

*Renal or hepatic impairment*
No formal studies have been conducted with Episalvan in patients with renal or hepatic impairment. No dose adjustment or special considerations are anticipated for patients with renal or hepatic impairment (see section 5.2).

*Elderly*
No dose adjustment is required.

*Paediatric population*
The safety and efficacy of Episalvan in children and adolescents under 18 years have not yet been established. No data are available.

Method of administration

For cutaneous application.
Fresh wounds should achieve haemostasis prior to application of Episalvan. If necessary, wounds (accidental wounds) should be cleaned according to standard procedure, using e.g. wound antiseptic solution, prior to application of Episalvan.

Episalvan is for single use only.

## 4.3 Contraindications

Hypersensitivity to the active substance or to the excipient listed in section 6.1.

## 4.4 Special warnings and precautions for use

Wound infection

Episalvan gel is sterile. However, wound infection is an important and serious complication that can occur during wound healing. In the case of infection, it is recommended to discontinue treatment with Episalvan. Additional standard treatment may be required (see section 4.5).

Wound size

The mean wound size treated with Episalvan in clinical studies in split-thickness skin graft donor site wounds was 40.7 $cm^2$ (range 8-300 $cm^2$). In the Grade 2a burn wound study, the mean wound size treated with Episalvan was 108 $cm^2$ (range 23-395 $cm^2$).

Duration of use

There is no information available on clinical use of Episalvan for more than 4 weeks.

Partial thickness burn wounds

Repeated critical assessment of burn depth and healing progression is needed. Wounds that are assessed as unable to heal within an acceptable time frame may need surgical measures (e.g., split-thickness skin grafting) to reduce the risk of hypertrophic scarring.

Other wound types

There is no clinical experience from the use of Episalvan for the treatment of chronic wounds, e.g. diabetic foot ulcers, venous leg ulcers or wounds in patients with epidermolysis bullosa.

Birch pollen allergy

Episalvan is safe to use for people who are allergic to birch pollen, as these allergens are not present in Episalvan.

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

No interaction studies have been performed. Since the systemic exposure of Episalvan following cutaneous application is negligible no interaction with systemic treatments is expected. Interactions with topical products have not been investigated in clinical trials. Other topical products should not be concomitantly used together with Episalvan but rather sequentially or alternatively depending on the clinical need.

## 4.6 Fertility, pregnancy and lactation

Pregnancy

No studies in pregnant women have been conducted.

No effects during pregnancy are anticipated, since systemic exposure to Episalvan is negligible. Episalvan can be used during pregnancy.

Breast-feeding

No data are available to evaluate whether Episalvan is excreted into human milk.

No effects on the breastfed newborn/infant are anticipated since the systemic exposure of the breast-feeding woman to Episalvan is negligible. Episalvan can be used during breast-feeding, unless the chest area is subject to treatment.

Fertility

Fertility studies have not been conducted. No effects on human fertility are anticipated, since the systemic exposure is negligible.

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

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

### 4.8 Undesirable effects

Summary of the safety profile

The most frequently observed adverse reactions were wound complication (in 2.9% of patients), pain of skin (2.5%) and pruritus (1.3%). Adverse reactions were administration site reactions only. Wound complication adverse reactions such as wound infection and wound necrosis are complications of healing of partial thickness skin wounds and can be serious (see section 4.4).

Tabulated list of adverse reactions

In the following table, adverse reactions are listed by MedDRA system organ class and preferred term. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

The frequency of adverse reactions is defined as follows: 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).

**Table 1: Adverse reactions reported in clinical trials**

| System organ class | Common | Uncommon |
|---|---|---|
| Infections and infestations | | Wound infection |
| Immune system disorders | | Hypersensitivity |
| Skin and subcutaneous tissue disorders | Pain of skin<br>Pruritus | Dermatitis<br>Rash pruritic<br>Purpura |
| General disorders and administration site conditions | | Pain |
| Injury, poisoning and procedural complications | Wound complication* | |

* Wound complication comprises different kinds of local complications such as post-procedural complications, wound necrosis, wound secretion, impaired healing, or inflammation of wound.

In addition, there is one case report of contact dermatitis reported from a literature in a patient after prolonged use of a topical birch bark extract containing cosmetic product.

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

Overdosing with Episalvan is unlikely: in patients in which wound sizes >300 $cm^2$ were repeatedly treated with Episalvan, no betulin plasma levels could be detected.

No data have been generated to study the effect of accidental ingestion of Episalvan.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Preparation for treatment of wounds and ulcers; ATC code: D03AX13.

Mechanism of action and pharmacodynamic effects

The active substance accelerated re-epithelialization in an *in vitro* wound scratch assay using human primary keratinocytes at the dosage of 1 µg/ml, and in a porcine *ex vivo* wound healing model at the dosage of 10 µg/ml. The precise mechanism of action of the active substance in wound healing in humans is not known.

Clinical efficacy and safety

Three Phase III studies were conducted to assess the efficacy and safety of Episalvan in the treatment of partial thickness wounds of the skin: two studies which investigated split-thickness skin graft donor site wounds, which included a total of 219 patients (ITT: N=217), and one further study in 61 patients with Grade 2a burn wounds (ITT: N=57). Patients with deeper burn wounds (Grade 2b) were not included.

The 219 patients with split-thickness skin graft donor site wounds had a mean age of 53 years; their donor site mean wound size was 81.5 $cm^2$. In the burn wound study with 61 patients, the mean study wound area was 216 $cm^2$; the total burn injury of these patients was larger and affected 5.8% of the total body surface area.

The Phase III studies were blindly evaluated, prospective, intra-individually controlled, randomised, multicentre trials. The target wound area of each patient was divided into two treatment areas of approximately the same size; the treatment allocation to the two halves of the wound (distal vs. proximal) was determined by randomisation (in the burn trial, two similar wounds could be used). Episalvan plus wound dressing was applied to half of the wound area, and the same kind of non-adhesive wound dressing alone was applied to the other half as the control in the split-thickness skin graft donor site studies. In the Grade 2a burn wound study an octenidine containing antiseptic wound gel and fatty gauze dressing were used as control. Application was at each wound dressing change every third to fourth day until full wound closure up to 28 days for the split-thickness skin graft trials, and every other day up to 21 days for the Grade 2a burn trial. Photographs of the wound were taken at each visit for the blinded evaluation.

The primary endpoint for the two split-thickness skin graft trials was the intra-individual difference in time to wound closure (at least 95% epithelialisation) based on blinded photo evaluations. Median time to wound healing was 14 days. Wound halves treated with Episalvan healed faster than the

wound halves treated with standard of care (mean 1.1 days according to primary endpoints, p<0.0001, two-sided paired t-test).

**Table 2: Overview of efficacy results: intra-patient difference in time to wound closure**

| **Mean intra-patient difference in time to wound closure (95% epithelialisation)** | **Split-thickness skin graft donor site wound studies (pooled)** | **Grade 2a burn wound study** |
|---|---|---|
| | **N=217** | **N=57** |
| Observer-blinded photo assessment (blinded read), mean expert evaluation | | |
| primary blinded read / very conservative calculation (primary endpoint for STSG studies) | -1.1 days (CI: -1.5, -0.7) faster wound closure with Episalvan, p<0.0001[a] | -1.0 days (CI: -1.4, -0.6) faster wound closure with Episalvan, p<0.0001[a] |

[a] Based on 2-sided paired t-test
Intention-to-treat (ITT) data set.
'Primary' vs. 'secondary' blinded read: In the primary blinded read evaluation a rigorous quality check was implemented to assure blinding of the observers. In consequence a substantial number of photographs were excluded and not presented in the primary blinded read because of apparent gel residues. The secondary blinded read was conducted with all photographs presented to the blinded observers.
'Very conservative calculation' means that the first observation of wound closure was taken as time of wound closure. Difference in time to wound closure was set to 0 for photo series rated as 'not evaluable'. If wound closure was not observed in a wound half photo series, it was calculated to have occurred one day after the last photograph in the series.
'Less conservative calculation' differs from the 'very conservative calculation' in one aspect: If wound closure was not observed in a wound half photo series, it was calculated to have occurred not one day, but approximately 3 days later (the mean time interval between wound dressing changes in the studies).
CI: 95% confidence interval; MTWDC: mean time to wound dressing change; N: number of patients in the analysis set; STSG Split-thickness skin graft

The primary endpoint for the Grade 2a burn wound trial was the percentage of patients with earlier healing (at least 95% epithelialisation) based on blinded photo evaluations. Median time to wound healing was 7.3 days. Of the patients with a between-treatment difference in wound healing (N=35), the percentage of patients who showed earlier healing (primary endpoint) of their Episalvan treated wound half (85.7% [95% CI: 69.7%, 95.2%]) was higher than those who showed earlier healing of their standard of care control treated wound half (14.3% [95% CI: 4.8%, 30.3%]) (p<0.0001, binomial test).

In follow-up visits at 3 months and 12 months after the day of surgery or of burn injury the treated wound halves were found to be equal in the majority of patients with regard to pigmentation, redness, texture and hair growth of the regenerated epidermis. For a subset of patients blinded photo-evaluation indicated better results for Episalvan treated wound halves compared to standard of care in pigmentation, redness and texture of the former wound areas.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Episalvan in one or more subsets of the paediatric population for the treatment of skin injuries (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

Absorption

Episalvan gel is administered topically to skin wounds and shows poor absorption. Based on data from three clinical studies with a total of 280 patients, application of Episalvan gel to open wounds did not

lead to betulin plasma levels higher than natural background-levels originating e.g. from nutritional sources.

Since no biologically relevant levels of betulin were found in patients, no further studies related to distribution, biotransformation and elimination were performed.

### 5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, local tolerance, and phototoxicity. Repeated dose toxicity and local tolerance have been studied for up to 4 weeks. Toxicity studies of longer duration than 4 weeks have not been performed. The active substance was not genotoxic in *in vitro* assays.

Carcinogenicity and reproductive and developmental toxicity studies have not been performed.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sunflower oil, refined.

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

4 years.

Once opened, the product should be used immediately and be discarded after use.

### 6.4 Special precautions for storage

Store below 30°C.

### 6.5 Nature and contents of container

White collapsible aluminium tube, interior lacquered with epoxy phenolic coating, and with a sealing compound in the fold. The tubes are closed with a tamper-evident aluminium membrane and fitted with a white polypropylene screw cap. The tube is packed in a cardboard box.

Pack size: 1 tube containing 23.4 g gel.

### 6.6 Special precautions for disposal and other handling

No special requirements.

## 7. MARKETING AUTHORISATION HOLDER

Amryt GmbH
Streiflingsweg 11
75223 Niefern-Öschelbronn
Germany
tel +49 (0) 7233 9749 - 0
fax +49 (0) 7233 9749 – 210

Email: info.de@amrytpharma.com

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1069/001

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

Date of first authorisation: 14 January 2016
Date of latest renewal:

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

**ANNEX II**

**A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Amryt GmbH
Streiflingsweg 11
75223 Niefern-Öschelbronn
GERMANY

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.
An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

**A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**OUTER CARTON and TUBE**

## 1. NAME OF THE MEDICINAL PRODUCT

Episalvan gel
birch bark extract

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

1g gel contains: 100 mg birch bark extract (as dry extract, refined) from *Betula pendula/Betula pubescens*, corresponding to 72-88 mg betulin.

## 3. LIST OF EXCIPIENTS

Excipient: Sunflower oil, refined.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Gel
23.4 g

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Cutaneous use.
Read the package leaflet before use.
For single use only. Discard after use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store below 30°C.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Amryt GmbH
Streiflingsweg 11
75223 Niefern-Öschelbronn
Germany

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1069/001

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Episalvan gel

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**B. PACKAGE LEAFLET**

**Package leaflet: Information for the patient**

**Episalvan gel**
birch bark extract

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**




## 1. What Episalvan is and what it is used for

Episalvan gel is a herbal medicinal product which contains dry extract from birch bark.

It is used in adults for the treatment of skin wounds, resulting for example from grade 2a burn wounds or from surgical skin graft transplantation. There is no experience of the use of Episalvan for the treatment of chronic wounds, e.g. diabetic foot ulcers or venous leg ulcers.

## 2. What you need to know before you use Episalvan

**Do not use Episalvan**
- if you are allergic to birch bark or any of the other ingredients of this medicine (listed in section 6).

**Warnings and precautions**
Talk to your doctor or nurse before using Episalvan.

Episalvan does not contain birch pollen, so it may be used by people with birch pollen allergy.

Wound infection is a serious complication that can occur during the healing process.
Possible signs of a wound infection are that the wound begins to drain yellow or greenish fluid (pus), or that the skin around the wound becomes red, warm, swollen, or increasingly painful.

**Children and adolescents**
Do not give this medicine to children and adolescents under 18 years of age because there is insufficient experience of the use of Episalvan in these patients.

**Other medicines and Episalvan**
If you have an infection in the wound additional treatment may be required.

Tell your doctor or nurse if you are using, have recently used or might use any other medicines.

No studies have been performed to establish whether Episalvan will interact with other medicines. However, since the amount of Episalvan absorbed into the body is extremely low it is not expected that Episalvan will interact with other medicines.

No data are available on possible interaction between Episalvan and other medicines applied to the skin. Do not apply other products to the skin wound area at the same time of applying Episalvan.

**Pregnancy, breast-feeding and fertility**
No studies have been done on the effects of Episalvan on pregnant women, but since the absorption of this medicine into the body is extremely low, the risk to the unborn baby is negligible. Episalvan can be used during pregnancy.

It is not known whether Episalvan passes into human breast milk, but since the absorption of this medicine into the body is minimal, the risk to the baby is negligible. Episalvan can be used during breast-feeding, unless the chest area is being treated.

The effect of Episalvan on fertility has not been studied, but since the absorption of this medicine into the body is extremely low, it is not expected to have an effect on your fertility.

**Driving and using machines**
Your ability to drive and use machines will not be affected by this medicine.

## 3. How to use Episalvan

Always use this medicine exactly as your doctor or nurse has told you. Check with your doctor or nurse if you are not sure.

Method of administration
- If necessary, wounds should be cleansed using a suitable antiseptic solution prior to application of Episalvan
- Episalvan should be applied to the wound surface at a thickness of approximately 1 mm and covered by a sterile wound dressing.
- Re-apply the gel each time the dressing is changed, until the wound is healed.

Duration of use
Your doctor or nurse will tell you for how long you should use the gel. Episalvan should be used until the wound is healed or up to 4 weeks.
There is no experience from long-term use of Episalvan for more than 4 weeks.

**If you use more Episalvan than you should**
Episalvan is applied to the skin and the absorption into the body is minimal. This makes overdose very unlikely, even if applied to large skin areas and for a long period of time.

**If you forget to use Episalvan**
Do not use a double dose to make up for a forgotten dose. Apply Episalvan at the next planned change of the wound dressing, continuing with your normal routine.

**If you stop using Episalvan**
Episalvan should be used as advised by your doctor or nurse. Do not stop using it without consulting your doctor or nurse. If your wound shows no signs of improvement over time, talk to your doctor or nurse.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
Tell your doctor straight away if you notice any side effects including those listed below.

The most frequently reported side effects are:
**Common side effects** (may affect up to 1 in 10 people)
- complications in the wound healing process
- painful skin
- itching

Other side effects include:
**Uncommon side effects** (may affect up to 1 in 100 people)
- wound infection
- allergic reaction (hypersensitivity)
- skin irritation (dermatitis)
- itchy rash
- purple coloured rash
- pain

**Reporting of side effects**
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

## 5. How to store Episalvan

Keep this medicine out of the sight and reach of children.
Store below 30°C.

Do not use this medicine after the expiry date which is stated on the carton and tube after 'EXP'. The expiry date refers to the last day of that month.

This product is for single use only and once opened, the product should be used immediately. Discard the tube after first use.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

**What Episalvan contains**
The active substance is a dry extract from birch bark.
1 g gel contains: 100 mg extract (as dry extract, refined) from birch bark from *Betula pendula*, *Betula pubescens* as well as hybrids of both species (equivalent to 0.5-1.0 g birch bark), corresponding to 72-88 mg betulin.

Extraction solvent: n-heptane.

The other ingredient is refined sunflower oil.

**What Episalvan looks like and contents of the pack**
Episalvan is a colourless to slightly yellowish, opalescent gel.

Episalvan gel is packed in white collapsible aluminium tubes. The tubes are closed with a tamper-evident aluminium membrane and fitted with a white polypropylene screw cap.
The tube is packed in a cardboard box.

Pack size:1 tube of 23.4 g gel.

**Marketing Authorisation Holder and Manufacturer**
Amryt GmbH
Streiflingsweg 11
75223 Niefern-Öschelbronn
Germany
tel +49 (0) 7233 9749 - 0
fax+49 (0) 7233 9749 – 210
Email: info.de@amrytpharma.com

**This leaflet was last revised in**

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

**ANNEX IV**

**GROUNDS FOR ONE ADDITIONAL RENEWAL**

**Grounds for one additional renewal**

Based upon the data that have become available since the granting of the initial Marketing authorisation, the CHMP considers that the benefit-risk balance of Episalvan remains positive, but considers that its safety profile is limited for the following reasons:

For Episalvan limited safety information is available because of limited exposure due to limited marketing of the medicinal product. As of the DLP, Episalvan has been placed on the market in only one EU country.

Episalvan has not yet been commercially launched or placed on the market in any other EU country and thus, no post-authorisation data are currently available. Furthermore, no data on post-authorisation use in special populations were reported as no non-interventional studies, including market research and registries, have been conducted with Episalvan since the granting of the marketing authorisation.

Therefore, based upon the limited safety profile of Episalvan, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time.