5 September 2011
EMA/678094/2011

# EPAR type II variation for Improvac

## (Gonadotropin releasing factor (GnRF) analogue-protein conjugate)

## Procedure No. EMEA/V/C/136/II/009

## EU/2/09/095/001–006

### Scope:

Type II – Addition of a claim to the existing marketing authorisation

# Table of contents

# 1. Background information on the variation

## *1.1. Submission of the variation application*

On 11 May 2009 the European Commission granted a marketing authorisation for Improvac an immunological product (Gonadotropin releasing factor (GnRF) analogue-protein conjugate) indicated to induce antibodies against GnRF to produce a temporary immunological suppression of testicular function for use as an alternative to physical castration for the reduction of boar taint caused by the key boar taint compound androstenone, in entire male pigs following the onset of puberty.

Pursuant to Article 16 of Commission Regulation (EC) No. 1234/2008, the marketing authorisation holder, Pfizer Limited, submitted to the Agency on 2 September 2010 an application for a type II (No. C.I.6.a) variation for Improvac.

### 1.1.1. Scope of the variation

The current variation application is to add a claim to the existing marketing authorisation to allow a third dose of the product to be given 10 weeks or more after the second dose to entire male pigs intended for slaughter at heavy weights.

| Previous | Proposed |
|---|---|
| SUMMARY OF PRODUCT CHARACTERISTICS | SUMMARY OF PRODUCT CHARACTERISTICS |
| **4.5. Special precautions for use** | **4.5. Special precautions for use** |
| Special precautions for use in animals | Special precautions for use in animals |
| Only healthy animals should be immunised. Improvac has been shown to be safe in male pigs from 8 weeks of age onwards. The recommended time for slaughter is 4 to 6 weeks after the second injection. If pigs cannot be slaughtered within this recommended period the available trial data support that pigs may still be sent for slaughter up to 10 weeks after the second injection with minimal risk of boar taint. An increasing proportion will return to normal function after this time. | Only healthy animals should be immunised. Improvac has been shown to be safe in male pigs from 8 weeks of age onwards. The recommended time for slaughter is 4 to 6 weeks after the ~~second~~ **final** injection. If pigs cannot be slaughtered within this recommended period the available trial data support that pigs may still be sent for slaughter up to 10 weeks after the ~~second~~ **final** injection with minimal risk of boar taint. An increasing proportion will return to normal function after this time. |
| As skatole levels are not fully dependent on sexual status, both dietary and hygiene management procedures to reduce skatole levels are also important. | As skatole levels are not fully dependent on sexual status, both dietary and hygiene management procedures to reduce skatole levels are also important. |
| **4.9. Amounts to be administered and administration route** | **4.9. Amounts to be administered and administration route** |
| Subcutaneous use. | Subcutaneous use. |
| Entire male pigs from 8 weeks of age onwards should be vaccinated with 2 doses of 2 ml at least 4 weeks apart, with the second dose given 4 to 6 weeks prior to slaughter. In case of suspected misdosing, the animal should be revaccinated immediately. | Entire male pigs from 8 weeks of age onwards should be immunised with 2 doses of 2 ml at least 4 weeks apart, with the second dose **normally** given 4 to 6 weeks prior to slaughter. **If slaughter is intended to be later than 10 weeks after the second dose, for example when producing heavy slaughter pigs, a third dose should be given 4 to 6 weeks before the planned slaughter date.** In case of suspected misdosing, the animal should be reimmunised immediately. |
| Administer by subcutaneous injection in the neck, immediately behind the ear, using a safety vaccinator with a short needle to give 12 to 15 mm penetration. The needle should be directed perpendicular to the skin surface. Avoid introduction of contamination. Avoid injecting pigs | Administer by subcutaneous injection in the neck, |

| Previous | Proposed |
|---|---|
| that are wet and dirty. | immediately behind the ear, using a safety vaccinator with a short needle to give 12 to 15 mm penetration. The needle should be directed perpendicular to the skin surface. Avoid introduction of contamination. Avoid injecting pigs that are wet and dirty. |

# 2. Scientific discussion

## *2.1. Introduction and rationale*

In most European countries, pigs are typically slaughtered between 22 and 26 weeks of age and a two dose regimen of Improvac is adequate to allow for the management of both undesirable male behaviour (sexual and aggressive) and boar taint following the onset of puberty. In Italy and Spain, a large population of pigs are raised to much heavier weights for the production of specialist ham products and are not slaughtered until 40 weeks of age or more.

Application of the standard 2-dose Improvac regimen in such circumstances dictates that the second dose would have to be administered at approximately 36 weeks, well beyond the point at which undesirable male behaviour can become evident. In such cases it is desirable that a third dose regimen is available as an option to maintain immunological suppression of testicular function for this extended duration of androgenicity, to assure behavioural control and acceptable freedom from boar taint up to slaughter.

An approved three dose regimen would also allow pigs to be given an additional dose in the unusual event that they could not be sent for slaughter even by 10 weeks after the second dose e.g. due to unforeseen circumstances such as disease outbreak/transport strike. This is important not only for the maintenance of reduced boar taint but also from an animal welfare perspective, as pigs will be resuming testicular function (and starting to express typical male aggressive/sexual behaviour) at different times within their group.

## *2.2. Submitted studies to support the proposed SPC wording*

Data from three clinical studies evaluating the effect of a 3-dose regimen of Improvac to reduce boar taint in heavy weight pigs were submitted by the applicant. The first of these studies has not been presented to CVMP before and is regarded as the pivotal study including entire boars as a positive control group. The two other studies were previously provided in the authorisation dossier in the response to the list of questions received from the CVMP regarding duration of effect. Both studies were not considered as proof of concept because they did not include an entire boar control group. However both studies did allow a side by side comparison of a 3-dose regimen with the standard 2-dose regimen and they underscored the need for a 3-dose regimen across the extended period of androgenicity. These studies are now presented again as supportive to the pivotal study described in detail below.

| | |
|---|---|
| **Study** | Aim: To demonstrate that a third dose of minimum potency Improvac given more than ten weeks after an initial two dose course controlled boar taint in entire males for at least four to six weeks after administration of the third dose |
| **Animals** | Entire male pigs (Duroc cross) were allocated in 2 groups: non-immunised served as control and immunised with Improvac |
| **Administration** | Subcutaneous, 2 ml per dose |
| **Immunisation scheme** | Group 1: Saline, at 10 weeks of age, at 20 weeks of age and at 36 weeks of age.<br>Group 2: Improvac, at 10 weeks of age (D0); at 20 weeks of age (D70); and at 36 weeks of age (D182) |

| | |
|---|---|
| **Follow-up** | • Blood samples were taken from all pigs at first immunisation (D0); second immunisation (D70), 14 days (D84) and 5 weeks (D105) after the second immunisation; at third immunisation (D182), and 3 + 14 days (D196) and at slaughter 5 weeks after the third immunisation (D217-218); all pigs were slaughtered at 41 weeks of age<br>• Serum titres of anti-GnRF antibodies were measured by ELISA<br>• Testosterone was measured by HPLC with mass spectrometric detection<br>• Androstenone concentrations in fat were measured by HPLC with mass spectrometric detection<br>• Skatole/indole was measured using HPLC with fluorescent detection<br>• Daily clinical observations from D0, veterinary diagnosis and treatment of any clinical symptoms in pigs throughout the study (not related to the administration of Improvac)<br>• Clinical observations by examining veterinarian 25 to 71 minutes after each injection to monitor pigs for suspected adverse reactions |

A single dose of minimum potency Improvac followed by a second dose on study day 70 and a third dose 112 days later resulted in a substantial increase in antibody titres against GnRF. After both second and third injections, levels of antibodies increased and peaked somewhere between two and five weeks after injection (the exact peak was not determined) to geometric LS mean titre of GnRF antibodies of 529.1 U/ml and 435.8 U/ml after 2 weeks and of 292.9 U/ml and 431.4 U/ml after 5 weeks respectively. Differences in sera titres within the Improvac immunised pigs were found to be statistically significant when comparing titres at: second injection and third injection ($p<0.0001$), two weeks post second injection and two weeks post third injection ($p<0.0200$) and five weeks post second injection and five weeks post third injection ($p<0.0001$).

The testosterone sera results were consistent with the antibody results. At first and second injections, there were no significant differences between the treatment groups in terms of the percentage of pigs with serum testosterone levels below the limit of quantification (LOQ) (<0.1 ng/ml). From second injection onwards all of the entire males had a serum testosterone concentration above the LOQ. At the sampling time point two weeks after second injection the majority of pigs immunised with Improvac had a serum testosterone concentration below the LOQ. From two weeks post second injection onwards, the treatment group differences were significant ($P<0.0001$ at each time point).

The percentage of pigs immunised with Improvac with testosterone levels below the LOQ remained high (90 %) five weeks post second injection, dropped at third injection (43 %) and then increased again (96 %) two weeks post third injection. At the time of slaughter 91 % of pigs immunised with Improvac had a testosterone serum concentration below the LOQ. The low numbers of pigs with quantifiable testosterone data in the Improvac group did not permit a meaningful statistical analysis to be performed.

The percentage and number of pigs with belly fat concentrations of androstenone, skatole and indole were investigated. Only 2 % of entire boars (T01) compared to 99 % of Improvac immunised pigs (T02) had androstenone concentrations below the LOQ which was statistically significant ($P<0.0001$). There were too few animals with quantifiable data to conduct a meaningful statistical analysis on the concentration levels. Only 5 % of entire boars had skatole levels below the LOQ, whereas 30 % of Improvac immunised pigs had skatole levels below the LOQ being statistically significant ($P<0.0001$). Among pigs with quantifiable concentrations of skatole, the geometric LS mean concentration in entire boars was 63.9 ng/g compared to 17.4 ng/g in immunised pigs which was statistically significant ($P<0.0001$). All entire boars and immunised pigs had levels of indole in belly fat above the LOQ. The geometric LS mean was 114.9 ng/g compared to 22.5 ng/g in immunised pigs.

At slaughter, 100 % Improvac immunised pigs had belly fat concentrations of both androstenone and skatole well below the recognised thresholds (500–1,000 ng/g and 200 ng/g respectively) for risk of boar taint. A total of 99 % Improvac immunised pigs had fat concentrations of androstenone below the

LOQ of the method (200 ng/g). In contrast, 91.5 % and 17 % of non immunised entire boars had androstenone and skatole concentrations at or above these respective thresholds.

The statistical analysis of the chemical assay results was performed by comparing the proportion of animals per pen falling into specific categories using back transformed means. On this basis 100 % of Improvac immunised pigs showed low androstenone concentrations (<500 ng/g) compared to 5 % of entire males (P<0.0001), when low and medium concentrations were combined (<1,000 ng/g), the figures were 100 % of Improvac immunised pigs and 23 % of entire males (P<0.0001). Similarly, a statistically significant difference was found in the proportion of animals per pen showing a low skatole concentration (<100 ng/g), 100 % Improvac immunised pigs versus 64 % of entire male pigs (P<0.0001) and animals showing low to medium skatole concentrations (≤200 ng/g), 100 % of Improvac immunised animals versus 85 % of entire male pigs (P<0.0001).

No adverse events were observed following administration of the product.

The CVMP accepted that this study is pivotal for the type II variation in order to allow three times injection, e.g. for heavy weight pig production. The study shows the full capacity for Improvac to reduce the risk of boar taint up to slaughter because a comparison is made to entire boars at an age well beyond the point at which male odour becomes evident. All pigs in this study were slaughtered five weeks after the third injection at which stage the effects of Improvac were still present, reducing the risk of tainted meat significantly to a minimum. This study provides adequate support for the effect of three times Improvac immunisation at 10 weeks, 20 weeks and 36 weeks of age when animals were slaughtered at 41 weeks of age.

The first supportive clinical study to examine the effectiveness of two-dose and three-dose Improvac regimens in heavy slaughter weight pigs was already evaluated during the initial authorisation procedure. It showed that titres of GnRF antibodies were found to be elevated in both Improvac groups (injected twice and injected three-times) compared to physical castrates at the time of the third administration.

When summarising the results from both the pivotal clinical efficacy study and this supportive study it was evident that the trend was the same for both anti-GnRF titres at different time points and proportion of pigs with serum testosterone levels below level of quantification.

When a comparison was made at different time points after injection in both studies it was evident that the trends were the same for the two studies with respect to least square mean anti-GnRF levels when pigs were injected three times. Because no blood sampling occurred shortly after the second dose in the supportive study, no serological anamnestic rise in titre after the second injection could be measured but serological responses after the third injection were similar.

The proportion of pigs with serum testosterone levels below level of quantification showed the same trend in both studies as for levels of anti-GnRF. None of the pigs administered three doses of Improvac had belly fat concentrations of androstenone or skatole above the respective 500–1,000 ng/g or 200 ng/g thresholds. This indicated support to the results from the pivotal study.

The second supportive clinical study to examine the effectiveness of both a two-dose and three-dose Improvac regimens in heavy weight pigs was also already evaluated during the initial marketing authorisation procedure. It also showed that none of the pigs administered three doses of Improvac had belly fat concentrations of androstenone or skatole above the respective 500–1,000 ng/g or 200 ng/g thresholds.

**CVMP conclusion with respect to the type IB variation, SPC, section 4.5**

The applicant proposed to replace in section 4.5 of the SPC, Special precautions for use the word "second" with the word "final" in two sentences:" The recommended time for slaughter is 4 to 6 weeks

after the ~~second~~ **final** injection. If pigs cannot be slaughtered within this recommended period the available trial data support that pigs may still be sent for slaughter up to 10 weeks after the ~~second~~ **final** injection with minimal risk of boar taint. An increasing proportion will return to normal function after this time".

While no follow up data were provided after the third injection for longer than 5–7 weeks and in the pivotal 3x injection study pigs were slaughtered 5 weeks after the final injection, the data provided by the applicant supporting the 10 weeks duration of immunity (DoI) after 3x injection confirmed at least the same degree of physiological suppression of testicular function after 3x injection as for 2x injection, and were accepted by the CVMP. The proposed rewording of the SPC, section 4.5 therefore is supported.

**CVMP conclusion with respect to the type IB variation, SPC, section 4.9**

The applicant also proposed to amend section 4.9. Amounts to be administered and administration route of the SPC to insert advice for the administration of a third dose if slaughter is intended to be later than 10 weeks after the second dose. The CVMP suggested deleting the following part of the proposed revision in the SPC, Section 4.9 "**for example when producing heavy slaughter pigs**". Thereby the wording would be more concise. The suggested sentences in the SPC, Section 4.9 as proposed by the CVMP are:

"Entire male pigs from 8 weeks of age onwards should be immunised with 2 doses of 2 ml at least 4 weeks apart, with the second dose **normally** given 4 to 6 weeks prior to slaughter. **If slaughter is intended to be later than 10 weeks after the second dose a third dose should be given 4 to 6 weeks before planned slaughter date**. In case of suspected misdosing, the animal should be reimmunised immediately".

### *2.3. Safety Studies*

The safety of a third dose of Improvac has been demonstrated in the GLP Safety Study that was presented in the application for the initial authorisation in Part 3 of the dossier, which was evaluated and accepted during the initial authorisation procedure. It was concluded that three consecutive doses of Improvac targeted at a double strength conjugate content were well tolerated in young pigs (8 weeks of age).

### *2.4. Suitability of Improvac Batches Used*

The commercial conjugate used the approved Diphtheria toxoid (DT) and 2-10 GnRF peptide analogue.

The conjugate compositions in the batches used for all three of the three-dose regimen clinical studies and the target animal safety study were considered suitable.

The CVMP noted that as the second supportive clinical efficacy study was not conducted with a minimum potency batch this study could only at its best be regarded as supportive. All other batches were accepted in order to demonstrate the safety and efficacy for evaluation of this type II variation.

## 3. Benefit risk assessment

The benefit/risk balance of the product remains positive. In addition, the benefit arising from the third administration has increased for heavy weight pigs due to the maintenance of reduced boar taint and suppression of testicular function (with concomitant reduction in typical male aggressive/sexual behaviour).

No change to the impact on the environment is expected.

# 4. Conclusion

The CVMP considered that this variation, accompanied by the submitted documentation which demonstrates that the conditions laid down in Commission Regulation (EC) No. 1234/2008 for the requested variation are met, is approvable.

# 5. Changes to the community marketing authorisation

Changes are required in the following annexes of the Community Marketing Authorisation:

- Annex I, Annex IIIA and Annex IIIB.