10 November 2010
EMA/41755/2011

EPAR type II grouped variation for Improvac

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

EMEA/V/C/136/II/007/G

Scope:

Type II – Addition of behaviour claim

Type IB – Addition of anaphylactoid like reactions

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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 5 August 2010 an application for a Type II variation for Improvac. This was a grouped variation that included two procedures: one Type II (C.I.6.a) variation regarding the addition of a behaviour claim and one Type IB (C.I.3.a) for the addition of a warning regarding anaphylactoid like reactions.

1.1.1. Scope of the variation

Addition of behaviour claim and addition of warning of anaphylactoid like reactions.

Summary of Product Characteristics (SPC) changes:

Previous	Proposed
4.2 Indications for use, specifying the target species Induction of 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. Another key contributor to boar taint, skatole, may also be reduced as an indirect effect. The onset of immunity (induction of anti-GnRF antibodies) can be expected within 1 week post second vaccination. Reduction of androstenone and skatole levels has been demonstrated from 4 to 6 weeks post second vaccination. This reflects the time needed for clearance of boar taint compounds already present at the time of vaccination as well as the variability of response between individual animals.	4.2 Indications for use, specifying the target species Induction of 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. Another key contributor to boar taint, skatole, may also be reduced as an indirect effect. **Aggressive and sexual (mounting) behaviours are also reduced.** The onset of immunity (induction of anti-GnRF antibodies) can be expected within 1 week post second vaccination. Reduction of androstenone and skatole levels has been demonstrated from 4 to 6 weeks post second vaccination. This reflects the time needed for clearance of boar taint compounds already present at the time of vaccination as well as the variability of response between individual animals.

	Reduction of aggressive and sexual (mounting) behaviours can be expected from 1 to 2 weeks post second vaccination.
4.6 Adverse reactions (frequency and seriousness) When administered to pigs at the youngest recommended age (8 weeks), injection site swellings of up to 4x8 cm are very commonly observed. A gradual resolution of the local reactions occurs, but in 20-30 % of the animals these may persist for more than 42 days. When administered to older pigs (14–23 weeks of age) injection site swellings ranging from 2 to 5 cm in diameter are commonly observed, and injection site reactions at slaughter are commonly observed if the second vaccination is given only 4 weeks before slaughter. A transient increase in rectal temperature (post-vaccination hyperthermia) of around 0.5 °C may be observed during the 24-hours period post vaccination.	4.6 Adverse reactions (frequency and seriousness) When administered to pigs at the youngest recommended age (8 weeks), injection site swellings of up to 4x8 cm are very commonly observed. A gradual resolution of the local reactions occurs, but in 20-30 % of the animals these may persist for more than 42 days. When administered to older pigs (14–23 weeks of age) injection site swellings ranging from 2 to 5 cm in diameter are commonly observed, and injection site reactions at slaughter are commonly observed if the second vaccination is given only 4 weeks before slaughter. A transient increase in rectal temperature (post-vaccination hyperthermia) of around 0.5 °C may be observed during the 24-hours period post vaccination. **In very rare cases anaphylactoid type reactions (dyspnoea, collapse, cyanosis and hyper salivation associated with or without muscle twitching or emesis) have been observed within a few minutes after the first vaccination with duration up to 30 minutes. In a small number of animals death occurred following the reaction, however most animals recovered without treatment and did not appear to react to subsequent vaccinations.**
5. Immunological Properties The effects of immunisation derive from the reduction in testicular function resulting from reduced GnRF activity. This leads to reduced production and concentration of testosterone and other testicular steroids, including androstenone, one of the main substances responsible for boar taint. A reduction of typical male behaviour such as mounting and aggressiveness **when mixed with non-penmates** can be expected after the second vaccination.	5. Immunological Properties The effects of immunisation derive from the reduction in testicular function resulting from reduced GnRF activity. This leads to reduced production and concentration of testosterone and other testicular steroids, including androstenone, one of the main substances responsible for boar taint. A reduction of typical male behaviour such as mounting and aggressiveness can be expected after the second vaccination.

2. Scientific discussion

Type II (C.I.6)

Rationale for claim

Improvac is currently indicated for the reduction of boar taint compounds in entire male pigs after the onset of puberty. The applicant wished to add an additional claim to section 4.2 of the SPC indicating reduction of aggressive and sexual male behaviour. This additional claim will not necessarily represent an independent justification for product use and will not expand the population of pigs eligible for Improvac treatment. In reality any pigs for which the claim is relevant will also be at risk of boar taint. Control of such testicular function-related behaviours is, however, a true effect of the product and an attribute that may be important when choosing the best method of boar taint reduction for a particular farm, particularly with the increasing interest in entire boar production in some countries.

Behaviour of maturing male pigs during commercial rearing

Pubertal development in commercially farmed pigs can start from as young as 12 to 14 weeks of age with full sexual maturity usually achieved by approximately 6 to 7 months of age.

Entire male pigs are more aggressive than both female pigs and castrated males. They have a higher frequency of play fighting and mounting at a young age but, as they get older, play decreases and fighting can become more serious leading to potential welfare issues.

Aggression among pigs may be manifest broadly in two ways. Firstly, there is a brief period of fighting to establish rank when unfamiliar pigs are mixed. Secondly, there is longer-term aggression among pen mates which consists of brief threats, bites and butts that occasionally can escalate into more prolonged fights. This longer-term aggression often involves competition for a specific resource, especially feed.

Conjugate Content in batches used in presented studies

Batches used in the submitted behaviour studies were formulated to the standard commercial conjugate content (400 µg/2 ml dose). These batches were then tested for conjugate content and demonstrated a range of potency values.

Typical batches of intermediate potency are generally deemed suitable for use in field efficacy trials (Ph. Eur. 5.2.7.). Moreover, pig serology/testosterone/taint studies have shown that the minimum potency approved (300 µg/2 ml dose) is robust and that the physiological effect (testicular suppression/reduction of boar taint and aggressive and sexual behaviour) from a minimum potency regimen would be no different than from a target 400 µg/2 ml dose potency regimen.

Thus, the conjugate content in the batches used for the pivotal studies for this Type II variation were acceptable.

Study:	Title: Long-term effect of vaccination against gonadotropin releasing hormone, using Improvac, on hormonal profile and behaviour of male pigs Aim: To evaluate the long-term effect of Improvac on testicular function, boar taint control, and behaviour
Animals	Entire male pigs (Yorkshire x Landrace): animals were allocated in 2 groups of pigs; one that was vaccinated with Improvac and the other that served as non-vaccinated controls. Pigs were housed in the same pen by treatment and the experimental unit was the pen.

Admin.	Subcutaneous, 2 ml per dose
Immunisation scheme	1. Group: V1 at 15 weeks of age; V2 at 21 weeks of age 2. Group: V1 at 14 weeks of age; V2 at 18 weeks of age
Follow-up	• Pigs were group housed for either 16 weeks (Group 1) or 22 weeks (Group 2) after the second vaccination. From 115 kg live weight pigs were randomly split from 6 to 3 animals in a pen, such that a total of 8 pens were observed with respect to behaviour in the "heavy weight" pigs. • Behaviour was recorded by video from approx. 08:00 to 17:00h at 4 weeks; 6 weeks (Group 2) or 8 weeks (Group 1); 10, 13 and 15 weeks after the second vaccination. • Behaviour of pigs from Group 2 was also video recorded 19 and 21 weeks after the second vaccination. Recordings were made as "scan sampling" each minute. • Recordings included morning and afternoon feeding, cleaning and providing of straw • Percentage of time (time budget) spent on the following activities was observed: sleeping (lying down, resting); walking (sitting, standing, rooting, walking, running); eating (head in trough or waiting for food or drinking); social (interaction in a non-aggressive way); manipulating (nibbling or pushing or has another pigs ear or tail in the mouth); aggressiveness (giving and receiving head-knocks or bites); mounting • Expression of sexual behaviour was also examined in a 7-minute mating test, using a female pig in oestrus, performed 9 and 15 weeks after the second vaccination and at 21 weeks (Group 2).

Results:

Results from this study were presented to CVMP during the original application procedure.

The average percent of day time that entire male pigs and vaccinated pigs spent on social, manipulating, aggressive and mounting behaviour throughout the studied period was provided.

Manipulating, aggressive, mounting and social behaviour differed significantly between treatments (P=0.006, 0.016, 0.033 and 0.024, respectively). At the different testing occasions, manipulating, aggressive and mounting behaviour differed significantly between treatments at several occasions. Testing occasion within treatment did not significantly affect social and mounting behaviour (P>0.05). The aggressive behaviour in the entire male pigs decreased at testing occasion three (10 weeks after the second injection was given to the vaccinated pigs) and eventually became similar to the vaccinated pigs.

In the mating test, most of the tested entire male pigs quickly mounted a female pig in oestrus. However, none of the vaccinated pigs mounted a female during the test, except for few in the 1st group which attempted to mount at 15 weeks after the second injection. In conclusion, the male pigs vaccinated with Improvac showed significantly reduced aggressive and mounting behaviour (and sexual, social and manipulating behaviour) than entire male pigs. This reduction was observed from

the first observation time (4 weeks after the second vaccination) to the last observation time (21 weeks after the second vaccination).

Conclusions:

This study correctly included a positive control, as reduction of social, manipulating, aggressive and mounting behaviour were measured as reduction in Improvac vaccinates when compared to entire males after onset of puberty. As behavioural tests were made only from 4 to 21 weeks after the second vaccination, results do not provide any information on the onset of action. The time budgets (% of day time) for the presented behaviours were rather low, but this was to be expected in a stable social hierarchy in a pen including only few pigs being above 115 kg live weight. The use of video-recordings and one minute scans from 08:00 to 17:00h ensured a valid recording system, as it covered the overall daily activity pattern for pigs having diurnal activity. Pigs showed major activity in the morning between 08:00 and 10:00h and again in the afternoon from around 14:00 to 17:00h. One minute scans might have underestimated the level of especially aggressive interactions and mounting, as both occur as short lasting bouts not necessarily picked up via the scans. Video-recordings are however a robust method to record behaviour as they do not interfere with the animals and tapes can be analysed without any effect of the observer on results.

The fact that around 17 % of vaccinates expressed mounting behaviour when tested 15 weeks after the second injection was in agreement with the temporary effect of Improvac. As mentioned in the SPC, Section 4.5 it is recommended to send pigs to slaughter 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”.

It was therefore accepted that aggressive and mounting behaviour was reduced from 4 weeks after the second injection with Improvac.

Study:	Title: Immunocastration reduces aggressive and sexual behaviour in male pigs Aim: To evaluate the effectiveness of Improvac in suppressing aggressive and sexual behaviour of male pigs
Animals	Pigs (Yorkshire x Landrace) were allocated in 2 experiments 1. Experiment (Exp. 1) included: entire males; vaccinated pigs; physical castrates 2. Experiment (Exp. 2) included: entire males; vaccinated pigs Piglets within litter were randomly allocated to treatments at birth. Pigs were raised in single-sex pens with eight pigs per pen.
Admin.	Subcutaneous, 2 ml per dose
Immunisation scheme	1. Experiment (vaccinated pigs) : V1 at 15 weeks (8 weeks before slaughter) ; V2 at 19 weeks of age (4 weeks before slaughter) 2. Experiment (vaccinated pigs): V1 at 13-15 weeks of age (8-11 weeks before slaughter); V2 at 19-21 weeks of age (4 weeks before slaughter)

Follow-up	• Before the first injection, the pigs were weighed and the four heaviest in the pen were marked. These marked pigs were injected two weeks earlier than their lighter pen mates at both first and second vaccination. The heavy pigs were slaughtered 2 weeks earlier than their lighter pen mates. This reflected normal commercial practice i.e., pigs being sold to weight rather than to age. • Pigs from the heavy weight groups in both Exp. 1 and Exp. 2 were slaughtered at an average age of 24 weeks and the light weight groups at 26 weeks. Slaughter was performed on two occasions per pen, 2 weeks apart. All pigs from Exp.1 were mixed with unfamiliar pigs during transport and lairage to simulate normal transport and slaughter conditions. Pigs from Exp.2 were slaughtered without mixing with unfamiliar pigs during transport and lairage. • Behaviour (activity and social interactions) was recorded by direct observations at four occasions per pen, 1 week before and after the first injection, 1 week after the second injection and 1 week after reduction of the number of pigs per pen from 8 to 4 due to slaughter. • As pigs in each pen were injected two weeks apart, behaviour was recorded either 1 or 3 weeks after the second dose (half of the animals in the pen at each time point). All observations were performed between 10:00 and 15:30h. Nine observation rounds were made per pen and each pen was studied for a 10-min session per round. The observations were made by the same observer within each experiment. • The observations consisted of two kinds of sampling and recording: instantaneous scan samplings of activity behaviours, and continuous recording of frequencies of social interactions. Instantaneous scan samplings were performed at the beginning and end of each observation round. Between these scans frequencies of social interactions were recorded for a total of 8 min. thus one observation day gave 18 instantaneous scan samples and 72 min. of social interactions per pen. Sexual behaviour was recorded both at scans and frequency recordings. • Scan samplings included the following behaviour parameters: Eating, sleeping, standing, sitting, bite bars, contact, sexual. Social interactions included: sniffing, pushing, crowding, manipulating tail, manipulating ear, aggressive, mounting. • Skin lesions were recorded four times on each pig (before first injection, between first and second injection, at first slaughter occasion, after first slaughter occasion). Pigs were classified in two groups: with or without skin lesions.

Results:

Treatment did not significantly affect the time that pigs spent eating, resting, standing, sitting or biting bars at any observation occasion. Contact and sexual behaviour differed significantly between treatments at some observation occasions. According to the scan sampling before the first injection, physically castrated pigs had less social contact with each other than entire male pigs and Improvac vaccinated pigs (P = 0.004 and 0.021, respectively).

After the first injection, no difference between treatments in social contact was found. After the second injection, pigs vaccinated with Improvac spent less time on contact compared with entire male pigs (P = 0.011) but similar to physically castrated pigs (P = 0.579). The same result was also observed at the fourth observation occasion, when the number of pigs per pen was reduced from eight to four (P = 0.003 and 0.853, respectively). Before and after the first injection, no difference in sexual activity was found between treatments. After the second injection, the Improvac vaccinated pigs used less time performing sexual activity than the entire male pigs (P = 0.015), but similar time as physically castrated pigs (P = 0.587).

Before the first injection, social interactions did not differ significantly between treatments. However, there was a tendency that physically castrated pigs performed less aggressive and mounting interactions than the other pigs (P = 0.085 and 0.080, respectively). After the first injection, mounting frequency was significantly lower for physically castrated pigs than for entire male and Improvac pigs (P = 0.001 and 0.009, respectively). A tendency (P = 0.057) to lower aggressive interactions was also found for the physically castrated pigs in comparison to entire male and Improvac pigs (P = 0.049 and 0.019, respectively). At the observation occasion after the second injection, the number of aggressive and mounting interactions observed were fewer among Improvac pigs compared with entire male pigs (P = 0.009 and 0.001, respectively) but similar to physically castrated pigs (P = 0.667 and 0.806, respectively). The reduction in aggressive behaviour during the time period from before to after the second injection was 78% for Improvac pigs compared with 31% for entire male pigs. Those entire males that were heaviest tended to perform fewer mountings than their lighter pen mates at this observation occasion, whereas no difference in behaviour between the heavy and the light group was found for vaccinated (P = 0.373) or physically castrated pigs (P = 0.556). After reduction from 8 to 4 pigs per pen, Improvac pigs still were less aggressive and performed fewer mountings than entire male pigs (P = 0.024 and 0.001, respectively).

Before and after the first injection, percentage of pigs without skin lesions was higher for physically castrated pigs (74% and 78%) compared with entire male (48% and 39%) and Improvac pigs (36% and 40%) (P = 0.011 and 0.003). After the second injection, the percentage of Improvac pigs without skin lesions increased to 66% and was similar to physically castrated male pigs (74%), as compared to 46% for the entire male pigs (P = 0.024). After the reduction in number of pigs per pen from 8 to 4, more Improvac and physically castrated pigs were without skin lesions, 74% and 100% respectively, compared with 38% for entire male pigs (P = 0.001).

Treatment significantly affected skin lesions recorded at slaughter (P = 0.009; only recorded in the 1st batch). More entire male pigs had skin lesions (70%) compared with physically castrated pigs (30%) and Improvac pigs (46%). The frequency of skin lesions at the testing occasion just before the pigs were sent to slaughter did not significantly relate to skin lesions recorded at slaughter (r = 0.16 and P = 0.152).

After the second injection, Improvac pigs showed less non-violent social and aggressive behaviours than entire male pigs of the same age. Mounting was reduced to the same low level as in physically castrated pigs and more Improvac pigs were without skin lesions compared with entire male pigs. Pigs that received the second injection only 1 week before the observation day did not differ significantly in behaviour from those that received the injection 3 weeks before the observation day. Thus, the behaviour appeared to change soon (by one week) after the second injection and these changes remained until slaughter.

Conclusions:

This new study (not presented to CVMP before) was regarded as the pivotal study to support the claim with respect to reduction of aggressive and sexual (mounting) behaviours after the second injection with Improvac. The study included sufficient number of pigs in total and per pen to be representative

for a field situation, and delivery to slaughter twice per pen according to live weight of the pigs is a realistic situation. Results from this study seemed to be a "worst case" situation in order to detect aggressive and mounting behaviours as recordings were made between 10:00 and 15:30h. This observation schedule reflected a standard working day for staff more than reflects the daily activity pattern of pigs. Only the hours between 13:30 and 15:30h include main activity of these diurnal animals, therefore the overall levels of aggressive and mounting behaviours appeared to be underestimated compared to the situation in practice. It was notable that the level of aggressive and mounting behaviour in male pigs at the last recording was reduced to almost a third of the levels recorded with eight pigs per pen. This was however in good agreement with the increased space allowance while doubling the area per pig per pen after removing the first four pigs for slaughter. Reduction of aggressive and mounting behaviour in Improvac pigs when compared to entire males was consistent after the second injection, and the onset could be detected from one week post injection. Until the second injection is administered vaccinates behave as entire males, because the immunological suppression of testicular function only becomes effective after the second injection. Therefore in practice timing of the second vaccination is crucial as behavioural/welfare problems as well as boar taint problems tend to increase with the onset of maturity of pigs, which varies between genotypes, environments and management systems.

Reduction in the level of the skin lesions in Improvac vaccinated pigs compared to male pigs was not claimed; therefore results were regarded as supportive information. Reductions were consistent after the second injection, but the body lesion scores recorded at slaughter did not significantly relate to the lesions recorded in the pen just before pigs were sent to slaughter ($r = 0.16$). This meant that that the relevant causes and effects causing skin lesions were different in the pen and at slaughter. The main reason for this was mixing with unfamiliar pigs during transport and lairage before slaughter where fighting to establish a new rank order causes aggressive behaviour (predominantly in male pigs).

As a result of the above it was considered that male pigs injected with Improvac showed significantly reduced aggressive and mounting behaviour (and sexual, social and manipulating behaviour) than entire male pigs. This reduction was apparent by one week after injection of the second dose and until the last observation prior to slaughter (3 weeks after second dose).

Study	Title: The behaviour of male fattening pigs following either surgical castration or vaccination with a GnRF vaccine Aim: To compare the behaviour of male fattening pigs either physically castrated without anaesthesia within a week of birth (T1) or injected twice with Improvac later in life (T2)
Animals	Male pigs from 55 litters (EUROC hybrid x Pietrain) housed in a commercial German farm were included. Within the first week after birth piglets were randomly allocated to two groups: Group T1 were physical castrates; Group T2 were Improvac injected animals. At 10 weeks of age pigs were moved to the fattening unit and a total of 96 pigs per treatment were randomly selected and allocated to pens. T2 pigs were injected with the first dose of Improvac after allocation and the pen was the experimental unit.
Admin.	Subcutaneous, 2 ml per dose
Immunisation scheme	V1 at 10 weeks of age; V2 at 21 weeks of age (4-5 weeks prior to slaughter)

Follow-up	• Behaviour of pigs was studied from the beginning to the end of the fattening period (weeks 1-16) via video recordings once a week for 24 hours • Behavioural observations were focused on general activity (postures) and on social behaviour (including sexual and aggressive behaviour) • In order to analyse the development of the treatment groups, the fattening period was divided into four phases: Phase I (fattening weeks 1-4; pigs 10-13 weeks old), Phase II (weeks 5-8; pigs 14-17 weeks old), Phase III (weeks 9-12; pigs 18-21 weeks old) and Phase IV (weeks 13-16; pigs 22-25 weeks old) • In the fattening phases I-III (prior to 2nd vaccination), physical castrates (T1) were compared to entire males (T2) and thereafter (Phase IV) they were compared to fully immunized Improvac males. • Data on postures were scored from the 24-hour videos recorded in every week of the fattening period (16 weeks) using scan sampling with 5 minute intervals. • Social behaviour was analysed in weeks 2, 4, 6, 8, 10, 12, 14, 15 and 16 by three trained observers. In each of the 16 experimental pens, four pigs were randomly selected as focus animals and marked individually • On each observation day, behaviour was observed for 8 hours allocated in four blocks of 2 hours (A: 00:30-02:30, B: 07:30-09:30, C: 12:0-14:30 and D: 16:45-18:45). The number of displacing, head knocking, biting, fighting, quarrelling, playing, manipulating, mounting and mounting attempts were recorded

Results:

Overall, during the whole fattening period, injected pigs (T2) were more active than physical castrates (T1), indicated by a higher proportion of pigs standing (T1: 9.3%; T2: 10.74%; $P<0.023$). T2 pigs showed a significant decrease in standing and an increase of sitting and lying after the 2nd vaccination of Improvac. No significant effects of treatment on the total number of agonistic interactions ($P = 0.064$) and on biting and fighting ($P = 0.151$) were found. In T2 pigs the prevalence of aggressive behaviours decreased after the 2nd vaccination ($P<0.001$) to the same low level observed for T1 pigs until slaughter. T2 animals showed a higher level of mounting behaviour compared with T1 animals, but on a very low level. Treatment had no effect on the prevalence of positive social behaviours i.e., play and manipulating of pen mates.

Conclusions:

This study was very comprehensive with respect to collection of behavioural data and performed in grower pigs on a commercial pig farm. Higher general activity was found in the Improvac group (T2) until two weeks after the second injection, but in general although statistically significant it was not very biological relevant because differences were only around 2% of the overall activity. The second injection of Improvac was administered rather late during the fattening period (week 21 after birth equal to the end of Phase III in the study). Therefore Improvac vaccinated pigs were "entire males" for most of the fattening period, and this was reflected in the higher number of agonistic interactions compared to surgically castrates especially in growth phase III (although only marginal statistical significant, $P = 0.064$). After the second injection of Improvac agonistic interactions gradually decreased to the same level as for surgical castrates (over a two week period). Although behaviour was intensely recorded in blocks of time and over weeks it could be expected that blocks A and C did

not participate much to the results, as they both were within the sleeping periods of pigs (night time and mid day). The significant effect of block did not influence the overall effect of treatment though therefore exclusion of these observation periods would not have influenced the final results. In general the level of agonistic behaviour was rather low in the study but this could also be due to the fact that pigs were inactive for at least 50% of the time observed.

A significant effect of the interaction between treatment and fattening phase on aggressive behaviour was found. Paired comparisons revealed that T2 animals had a higher level of agonistic behaviour in phase III (before second Improvac injection) than the level in T1 pigs. This sets emphasis on the fact that timing of vaccination is crucial for the potential welfare benefit of the temporal immunological suppression of testicular function of male pigs. There is a conflict between the wish to keep daily live weight gain and lean growth as high as possible (in entire males) during most of the fattening period and the possible welfare problems raising entire males with increased male behaviour expressed.

Overall it was considered that the number of agonistic interactions was statistically significantly higher in "entire males" than in surgically castrated pigs during growth phase III (after onset of puberty, P=0.028) while the overall model for the whole fattening period was only marginal statistical significant (P=0.064). This was meaningful as pigs went through puberty during this growth phase while they still did not receive the second injection of Improvac.

More studies (which were already submitted in the original dossier of the product) were presented to support this new behavioural claim but their results were only supportive to the scope of the variation and therefore they are not presented in this report.

CVMP conclusion with respect to the SPC claim, Section 4.2

Results from the above three studies were accepted as relevant and sufficient to cover the proposed changes in the SPC, Section 4.2. Two of the three studies showed reduction of aggression and mounting from 1-2 weeks post the second injection of Improvac, while the third study studied the long term effect on aggression and mounting after 4 weeks only. Other submitted studies were regarded as only supportive either due to insufficiencies relating to the batches used or the methods by which pig behaviour was recorded to show reduction in male pig aggression and mounting.

Pivotal studies supported the fact that Improvac injected males behave like entire males until immunological suppression of testicular function becomes effective after the second injection. The degree of suppression of typical male sexual behaviour appeared to be more gradual than abrupt during the period after the second injection therefore timing of vaccination is crucial. Behavioural/welfare problems tend to increase with the onset of maturity, which varies between genotypes, environments and management systems. Administration of the second injection more than 4 weeks before slaughter would be beneficial to behaviour but would also conflict with lean carcass composition at slaughter as vaccinated pigs come closer to the composition of surgical castrated pigs the longer vaccinates are immunologically castrated.

It was noted that Improvac is indicated for male pigs from 8 weeks of age and pigs should be vaccinated with 2 doses at least 4 weeks apart, with the second dose given 4 to 6 weeks prior to slaughter. During the studies provided to support the additional efficacy claim, the first dose of Improvac was administered from at least 10 weeks of age and the second dose from at least 18 weeks of age. It is however also a fact that the most sensitive target group should be used to study the safety and efficacy of this immunological product. The most sensitive target group with respect to behaviour and stress physiological reactions was in pigs below 50 kg live weight. This was supported by results from use of Improvac in the field, where "anaphylactoid reactions" have been observed in very rare cases only after first injection (the primer).

The CVMP therefore considered that the submitted studies for this behavioural claim were a "worst case" situation and thus appropriate. If Improvac was administered to pigs at 8 weeks (primer) and again at 12 weeks (to effect) it would completely prevent the pigs coming into puberty (start from around 12-14 weeks of age in some breeds). Therefore the behaviour of vaccinates would simulate the behaviour of castrates throughout the production period. Such a vaccination schedule would therefore be very sensitive in order to prevent aggression and mounting while still leaving pigs to be slaughtered until 22 weeks of age without boar taint problems. But the negative consequences on production parameters such as live weight gain, feed conversion rate and lean carcass composition at slaughter would all be substantial using such a strategy.

In the studies provided here it was obvious that behavioural reductions in aggression and mounting only take on from 1-2 weeks after the second injection leaving the behavioural effects to be present during only the last period of production (2-4 weeks) before slaughter on the farm and during transport and hold at the slaughter plant.

The CVMP was of the opinion that the addition of the claim, that 'aggressive sexual (mating) behaviours are also reduced' was adequately supported.

CVMP conclusion with respect to the proposed amendment to the SPC, section 5

It was also acceptable to exclude the following part of the last sentence in the second paragraph: "when mixed with non pen mates".

Type 1B (C.I.3.a)

In addition to the Type II behaviour claim application the company also submitted a Type 1B (C.I.3.a) variation to add a warning regarding anaphylactoid like reactions in section 4.6 of the SPC.

CVMP conclusion with respect to the Type 1B variation, SPC, section 4.6

The CVMP confirmed the conclusions from the assessment of the first PSUR for Improvac. It was agreed that changes to the marketing authorisation were necessary and an amendment to the SPC, Section 4.6 was needed as follows: "In very rare cases anaphylactoid type reactions (dyspnoea, collapse, cyanosis and hyper salivation associated with or without muscle twitching or emesis) have been observed within a few minutes after the first vaccination with duration up to 30 minutes. In a small number of animals death occurred following the reaction, however most animals recovered without treatment and did not appear to react to subsequent vaccinations".

The CVMP recommended the implementation of this sentence in the warning section (4.6) of the SPC in line with the conclusions of the assessment of the first PSUR for the product.

3. Benefit-risk assessment

The benefit/risk assessment for the vaccine is unchanged.

4. Conclusion

The CVMP considered that this grouped 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.

No change to the impact on the environment is envisaged.

5. Changes to the community marketing authorisation

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

- Annex I, IIIA and IIIB.