CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board (MEB) in the Netherlands

Diacetylmorfine 75/100/150/200 mg,
poeder voor inhalatiedamp
and
Diacetylmorfine HCl 3 g,
Poeder voor oplossing voor injectie

DiacetylM BV, Amsterdam, The Netherlands

Diacetylmorphine and Diacetylmorphine HCl

This assessment report is published by the MEB following Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB. It reflects the scientific conclusion reached by the MEB at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation. This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

Registration number in the Netherlands: RVG 33463, 33464, 33465, 33466, 33647

16 January 2007

Pharmacotherapeutic group:	Opioids
ATC code:	N02AA09
Route of administration:	Intravenous and by inhalation
Therapeutic indication:	For use as adjunctive therapy in poorly functioning treatment-resistant patients with long-standing diacetylmorphine (heroin) dependency
Prescription status:	Prescription only
Date of first authorisation (national):	20 December 2006
Application type/legal basis:	Directive 2001/83/EC, Article 8(3)

For the Dutch version of the product information for healthcare professionals and users see the product information in the Medicines Data Bank on our web-site.
The English translation of the product information for healthcare professionals is attached to this report.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) has granted a marketing authorisation for as spelled in Dutch "*Diacetylmorfine 75/100/150/200 mg, poeder voor inhalatiedamp"* and "*Diacetylmorfine HCl 3g, poeder voor oplossing voor injectie"*, from Di-AcetylM BV (Amsterdam, The Netherlands). The products have been authorised on 20 December 2006. The product is indicated for use as adjunctive therapy in poorly functioning treatment-resistant patients with long-standing diacetylmorphine (heroin) dependency (DSM IV -TR 304.00), who administer this compound by injection/inhalation on a (nearly) daily basis, who have failed to respond to treatment in at least one regularly attended methadone maintenance programme and who are currently treated with methadone.

Diacetylmorphine should be self-administered under supervision only in specialized treatment units, approved for this purpose by the Dutch Ministry of Health, Welfare and Sports. The treatment units will provide clean, suitable facilities, as well as all requirements and medical assistance necessary for safe self-administration of diacetylmorphine. A comprehensive description of the indications and posology is given in the Summary of Product Characteristics (SPC).

The marketing authorisation is granted based on article 8(3) [full application] of Directive 2001/83/EC.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice

The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for these type of products at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

POWDER FOR SOLUTION FOR INJECTION

Active substance

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance to be protected, while at the same time allowing the marketing authorisation holder to take full responsibility for the medicinal product and the quality and quality control of the active substance. Competent Authorities have access to the complete information that is necessary to evaluate the suitability of use of the active substance in the medicinal product

Manufacture of the active substance

Diacetylmorphine is prepared from natural sourced morphine alkaloid starting material via a one-step acetylating and subsequent crystallization process. The drug substance has been adequately characterized. In general, sufficient information has been provided on the synthesis. Also, for the starting material and solvents acceptable specifications have been adopted. The drug substance is a white to off white powder that is freely soluble in chloroform, sparingly soluble in alcohol, slightly soluble in diethyl ether and very slightly soluble in water. Diacetylmorphine contains five chiral centres and is obtained solely from natural sourced morphine alkaloid from the poppy (Papaver Somniferum). Only one form ((-))morphine has been found to occur in the poppy. Diacetylmorphine HCl exists only in one polymorphic form. A hydrate with one water molecule is used for the product at issue.

Quality control of the active substance

The drug substance specification is in line with the British Pharmacopoeia (BP) monograph on *Diacetylmorphine HCl* and European Pharmacopoeia (Ph.Eur.)* requirements. The specification is acceptable in view of the route of synthesis and the various (European) guidelines. Batch analysis data showing compliance with the specification have been provided.

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

** Ph.Eur. and BP are official handbooks in which methods of analyses with specifications for substances/products are laid down by the authorities of the European Union and United Kingdom respectively.*

Stability tests on the active substance

Stability data have been obtained during storage at 25°C/60% RH and 30°C/65% RH. The drug substance was packaged in the commercial packaging, i.e. double LDPE bags in HDPE containers. The solid drug substance is stable with respect to degradation. Based on the data provided, the recommended retest period of two years is justified. No special storage temperature is required, but the substance must be stored in the original package. Additional stability data further supporting the retest period will be provided by the active substance manufacturer.

Medicinal Product

Composition

The product is formulated as a powder for solution for intravenous injection. The powder is packaged into sterile, colourless, 30 ml hydrolytically class 1 glass vials, with grey sterile siliconised bromobutyl rubber stoppers and white flip-off (Al/PP) seals. Each vial contains the lyophilized active ingredient diacetylmorphine HCl in an amount of 3 gram. The vial is intended for multiple use.

Pharmaceutical development

The development of the product is satisfactory performed and explained. The vials contain a cake of 3 gram lyophilized diacetylmorphine HCl. The drug product does not contain excipients. The packaging is usual and suitable for the product at issue. However, although the vials are not intended to be provided to patients, the availability of only a pack-size of 3 grams may result in relative large amounts to be discarded at the end of the day. This pack-size therefore needs further discussion and the marketing authorisation holder has committed to provide further substantiation of the 3 gram pack-size based on the average amount of diacetylmorphine HCl needed and historic data regarding the average amount discarded. The marketing authorisation holder has also committed that, if based on these data, introduction of (a) smaller pack size(s) is deemed necessary by the MEB, such pack-sizes will be introduced.

Manufacturing process and quality control of the medicinal product

The powder is prepared by a lyophilization process of a solution of Diacetylmorphine HCl in water. The lyophilized powder cannot be terminally sterilized and therefore the solution is filtrated through a bacteria-retentive filter prior to lyophilization and aseptic processing. The manufacturing process has been sufficiently validated. The effectiveness and reproducibility of sterilizing vials and stoppers, used in the aseptic filling, will be further validated post approval.

The product specification for the powder includes tests for appearance, identity, assay, degradation, sterility, endotoxins, water, and uniformity of dosage units. A test on particulate matter will be included post-authorisation. Batch analysis data have been provided on three batches. Compliance with the release requirements is demonstrated.

Stability tests on the finished product

The shelf-life and release specifications are identical and are based on the British Pharmacopoeia (BP)* monograph for *Diamorphine Injection* and requirements of the European Pharmacopoeia (Ph.Eur)*. The product has been stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). No increase in degradation is seen. All results are within specification. Based on the data provided, the claimed shelf-life of two years is acceptable. No special storage temperature is required.

With regard to the shelf-life after reconstitution, batches were tested after 1, 25 and 38 months of storage. In-use tests were performed at 1, 2, 4, 6 and 24 hours. Also antimicrobial effectiveness was determined according to Ph.Eur. 5.1.3 (except that Aspergillus niger was replaced by Escherichia coli). The solution is stable for 24h after reconstitution, even after the product had been stored for 38 months. Based on the data provided, the claimed shelf-life of 12 hours after reconstitution when stored below 25°C is justified.

** Ph.Eur. and BP are official handbooks in which methods of analyses with specifications for substances/products are laid down by the authorities of the European Union and United Kingdom respectively.*

POWDER FOR INHALATION VAPOUR

Active substance and excipient

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance to be protected, while at the same time allowing the marketing authorisation holder to take full responsibility for the medicinal product and the quality and quality control of the active substance. Competent Authorities have access to the complete information that is necessary to evaluate the suitability of the use of the active substance use in the medicinal product.

Manufacture of the active substance

Diacetylmorphine is prepared from natural sourced morphine alkaloid starting material via a one-step acetylating and subsequent crystallization process. The drug substance has been adequately characterized. In general, sufficient information has been provided on the synthesis. Also, for the starting material and solvents acceptable specifications have been adopted. The drug substance is a white to off white powder that is freely soluble in chloroform, sparingly soluble in alcohol, slightly soluble in diethyl ether and very slightly soluble in water. Diacetylmorphine contains five chiral centres and is obtained solely from natural sourced morphine alkaloid from the poppy (Papaver Somniferum). Only one form ((-))morphine has been found to occur in the poppy. The manufacturing to Diacetylmorphine does not cause a change in stereochemistry. A study of polymorphic forms has been initiated by the active substance manufacturer.

Quality control of the active substance and excipient

Diacetylmorphine base is not described in a pharmacopoeia. The drug substance specification is in line with the British Pharmacopoeia (BP)* monograph of *Diacetylmorphine HCl* with regard to related substances and is in line with general European Pharmacopoeia (Ph.Eur.)* requirements. The specification is acceptable in view of the route of synthesis and the various (European) guidelines. Batch analysis data showing compliance with the specification have been provided.

The excipient caffeine anhydrate is in compliance with the requirements of the Ph.Eur. monograph on this substance.

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, thus a theoretical risk of transmitting TSE can be excluded.

** Ph.Eur. and BP are official handbooks in which methods of analyses with specifications for substances/products are laid down by the authorities of the European Union and United Kingdom respectively.*

Stability tests on the active substance

Stability data have been obtained during storage at 5°C and 25°C/60% RH. The drug substance was packaged in the commercial packaging, i.e. double LDPE bags in HDPE containers. The solid drug substance is stable with respect to degradation. Based on the data provided, the recommended retest period of one year is justified. The claimed storage temperature of 5°C (± 3ºC) is acceptable.

Medicinal Product

Composition

The product is formulated as a powder for inhalation after volatilization. The powder for inhalation vapour is packaged in one sachet per dosage unit. The material of the sachets consists of aluminium foil with polyethylene coating on the inside and paper coverage on the outside.

Pharmaceutical development

The development of the product is performed and explained satisfactory. The sachets contain diacetylmorphine and caffeine anhydrate. Caffeine is the sole excipient and serves as a volatilization enhancer and stabilizer. The packaging is usual and suitable for the product at issue.

Manufacturing process and quality control of the medicinal product

The two ingredients are blended to a homogeneous bulk mixture. This bulk mixture is used for filling the sachets of all strengths. The bulk mixture can be stored for two months. A stability study according to relevant guidelines will be initiated to further justify the bulk holding time. The manufacturing process has been sufficiently validated.

The product specification includes tests for appearance, identity, assay, degradation, and uniformity of dosage units. Microbial limit testing of the powder is not deemed necessary, in view of the nature of the sachets. Batch analysis data have been provided on three batches. Compliance with the release requirements is demonstrated.

Stability tests on the finished product

The shelf-life limits are based on the British Pharmacopoeia (BP)* monograph for *Diacetylmorphine Injection*. The product has been stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). Results at the accelerated conditions showed an out of specification increase of impurities. All stability results at normal conditions were within the specification. Addition of a test on moisture was asked for. Therefore, in the ongoing stability programme a test of moisture content will be performed at start and end of shelf-life.

Based on the data provided, the claimed shelf-life of two years is justified. A storage temperature below 25°C is required.

** The BP is an official handbook in which methods of analyses with specifications for substances/products are laid down by the United Kingdom.*

II.2 Non clinical aspects

Good Laboratory Practice

The non-clinical assessment was based on a review of the available literature provided by the marketing authorisation holder. As the non-clinical studies referred to in this review were not performed as part of a registration dossier to be composed, no a priori quality standards according to Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC) were set.

Pharmacology

The effects observed after a dose of diacetylmorphine most likely resulted from a combination of interactions of diacetylmorphine, 6-monoacetylmorphine and morphine on mainly μ-, but also δ- and κ-opiate receptors. The extent to which each compound contributes in a certain biological effect depends on the route of administration, time after administration, species or strain used and the involvement of the different opiate receptors in the effect studied.

Inhalation of diacetylmorphine is very efficient in the species studied and gives rise to pharmacological effects comparable to those seen after administration of diacetylmorphine via other peripheral routes and inhaled diacetylmorphine acts via the same types of opiate receptors as diacetylmorphine administered via other peripheral routes.

Diacetylmorphine induced analgesia in Rhesus monkeys. In ICR mice using analgesia, as a measure to determine the biological effect, diacetylmorphine appeared somewhat less potent by inhalation compared to intravenous (i.v.) administration. The antinociceptive effects of inhaled diacetylmorphine were completely antagonized by the μ-opiate receptor antagonist naloxone, but not by the κ-opiate antagonist nor-binaltorphimine or the δ-opiate receptor antagonist naltrindole.

Reinforcing behaviour in rats induced by diacetylmorphine is critically dependent on μ1-opiate receptors, but δ-opiate receptors are also involved. κ-opiate receptors do not seem to play a role in the reinforcing effects of diacetylmorphine. Also rhesus monkeys readily and reliably developed self-administration behaviour of smoked diacetylmorphine in a few training days.

Cardiovascular effects were studied in pentobarbital anaesthetized artificially ventilated intact dogs using a crude heroin preparation that contained 55 % diacetylmorphine and 25 % of another substance, most probably morphine. The main effect of this diacetylmorphine preparation was an instantaneous strong decrease in cardiac output, a moderate decrease in peripheral resistance together resulting in a strong decrease in arterial pressure. The heart rate decreased also, but more slowly. Effects of diacetylmorphine on respiration and heart rate were also studied in conscious rhesus monkeys. Doses as low as 0.03 mg/kg intramuscularly (i.m.) produced a statistically significant decrease in minute volume, reaching a decrease of more than 50 % at a dose of 0.3 mg/kg i.m. The heart rate decreased only at higher doses, reaching significance at a dose of 0.3 mg/kg i.m. Both the effect on respiration and the effect on the heart rate were antagonized by the mixed μ- and κ-opiate antagonist quadazocine

Pharmacokinetics

The available preclinical literature on the pharmacokinetics and the metabolism of diacetylmorphine is very limited and scattered. However, the data available are sufficiently consistent at least qualitatively. Diacetylmorphine is rapidly metabolised and distributed. The metabolism is largely extra-hepatic. Diacetylmorphine is converted into 6-monoacetylmorphine and subsequently into morphine and morphine-3-glucuronide as shown in the dog. Diacetylmorphine has a large volume of distribution, indicating that a relative large part of an applied dose is temporarily stored in tissues. The long half-life of diacetylmorphine found in dogs indicates that tissue-stored diacetylmorphine is released again into the circulation. After administration of diacetylmorphine, a mixture of diacetylmorphine and its metabolites is present in a time-dependent and tissue dependent fashion. The resulting biological effect will depend on the tissue involved and on the time since administration and will be the weighed sum of the activities of all components.

Toxicology

At low doses the classical opiate-like pharmacological effects appear while at higher dosages, sedation, respiratory depression and convulsions are induced, leading to death at high dosages.

There are no elaborate repeated dose animal toxicity data on diacetylmorphine available to allow a meaningful risk assessment on the basis of animal data. Target organs of toxicity that are identified and that indicate the toxic risk of diacetylmorphine use for humans are the central nervous system (altered motor behaviour, respiratory depression, ultimately leading to death and/or convulsions), the skeletal muscle (degenerative myopathy in the soleus muscle), and the testes (atrophy of the germinal epithelium). In addition, the immune system (changes in lymph nodes, the spleen and in immunocompetent cells in humans) was a target organ for diacetylmorphine and morphine, the major metabolite of diacetylmorphine,

indicating an immunotoxic risk of diacetylmorphine use. This risk was emphasized by effects seen on cultured mouse splenocytes. Many of the observed effects occur at pharmacological doses. Therefore, adverse effects as seen in the animal studies may be considered clinically relevant.

Diacetylmorphine has the potential to adversely effect spermatogenesis and thereby male fertility. Female fertility was not thoroughly investigated, but limited data do not indicate a strong effect by diacetylmorphine. Diacetylmorphine is embryotoxic and induces loss of embryo's and fetal death. Mortality was also seen in offspring the first days after birth and postnatal development was adversely affected both structurally and functionally. The neuroteratogenic potential is manifested in various brain regions affecting an array of neurotransmitter systems with functional behavioural consequences. A No Observed Effect Level (NOAEL) for the effects on embryonic, pre- and postnatal toxicity was not found and is below 0.5 mg/kg subcutaneously; no data on exposure at this dose is available. Yet, this dose is within the pharmacological range. Therefore, the reproductive toxicity findings should be considered clinically relevant.

In pregnant and lactating Rhesus monkeys, exposure *in vivo* to diacetylmorphine increased the frequency of chromosomal abberations and the number of sister chromatid exchanges in the white blood cells, both in the mothers and in the babies, indicating higher fragility of desoxyribonucleic acid (DNA) and increased risk for mutational events. The results of this investigation correspond with those of several studies on addict populations, and demonstrate that under these conditions, diacetylmorphine is a clastogenic compound. In summary, it can be concluded that diacetylmorphine and/or its metabolites indirectly induce or enhance chromosome and DNA damage *in vivo*, in animals and humans.

No specific studies in animals are available to assess the carcinogenic potential of diacetylmorphine. Therefore, it is not possible to make a risk assessment from animal studies. However, there are data in the literature indicating increased sensitivity of diacetylmorphine users to attract cancer.

There are no data indicating that local toxicity is a concern.

The package of pre-clinical safety studies presented in the literature overview is limited with limited utility. The main reason for this is that the available studies were not performed as part of a formal drug development as suggested by relevant guidelines, but they were performed as scientific investigations. This means that the studies cited in this overview do not comply with guidelines with regard to characterization of the test compound, duration of treatment, parameters measured, confirmation of level of exposure to the test compound and conduct according to Good Laboratory Practices. In addition, hardly any study was done in non-rodents, the route of administration was not always relevant to the intended human use of diacetylmorphine (intravenous or by inhalation). Specifically the lack of inhalatory toxicity studies on diacetylmorphine and caffeine can be seen as an omission. Also, carcinogenicity studies have not been performed with diacetylmorphine. Subsequently, the non-clinical risk assessment is incomplete and has mainly to be based on clinical experience. Yet, also taking note of the proposed indication, the MEB concluded that additional data from non-clinical studies would not alter the risk-benefit balance decisively.

Environmental risk assessment

Diacetylmorphine is intended as a substitute for products obtained by heroin addicts on the illegal market. The approval of this product will not result in a significant increase in the total quantity of diacetylmorphine released into the environment. It does not contain any component that results in additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Quality of clinical studies, compliance with GCP

The MEB has been assured that GCP standards were followed in an appropriate manner in the studies conducted. The formulation of the batches used in key clinical studies are considered equivalent to that proposed for marketing.

Clinical Pharmacology

Pharmacodynamics

Diacetylmorphine belongs to the opioid class of drugs and part of its pharmacologic effects are produced by its well-known metabolite morphine. Pharmacodynamic (PD) effects of diacetylmorphine are well-known in the context of its use as a drug of abuse. Opioids including diacetylmorphine stimulate μ opioid receptors and affect a wide range of physiological systems. They produce analgesia, affect mood and rewarding behaviour, and alter respiratory, cardiovascular, gastrointestinal, and neuro-endocrine function. It is especially the mood and rewarding behaviour effect that drives the patients to repeated drug use.

Most of the known diacetylmorphine PD effects are acquired from studies on street heroin that is sometimes contaminated with toxic agents. In this application dossier a pure industrial standard diacetylmorphine has been used, which may lead to fewer unexpected long term safety risks. Small changes in most PD parameters were observed in this population of very experienced diacetylmorphine abusers.

Lung function
Oxygen saturation and lung function were negatively affected by diacetylmorphine, but to a minimal extent only in this population of chronic diacetylmorphine users in a controlled administration programme. Long term diacetylmorphine use, in a gradually ageing population that uses a variety of prescribed and non-prescribed drugs, may have negative consequences for the respiratory system, although this was not shown in a shorter term PD study. Lung function will be addressed in the regular PSUR cycle.

Electrocardiogram (ECG)
Diacetylmorphine did not have a detrimental impact on QT/QTc intervals in a group of subjects who used methadone concomitantly. Selection bias of less vulnerable patients or tolerance could have led to the lack of expected effects with methadone. However, concomitant illegal cocaine use was correlated to an increase in QT/QTc interval. Therefore, patients may not be at risk of QTc prolongation because of diacetylmorphine use itself, but because of concomitant QTc prolonging drug use such as cocaine, ethyl alcohol and methadone.

Pharmacokinetics

A limited clinical pharmacokinetics (PK) programme existing of two clinical pharmacology studies was submitted, which is acceptable in view of the existing knowledge on diacetylmorphine and its major metabolite morphine in the public literature.

Analytical Methods
Bio-analytical methods for diacetylmorphine and its metabolites were well-described and validated over a concentration range of 5–500 ng/mL for all analytes, with a total recovery of diacetylmorphine of around 90% and with acceptable precision and accuracy (<20% at the Lower Limit of Quantification (LLQ)). Diacetylmorphine was kept stable by keeping the samples cool (-30°C) and at relatively low pH (<5.2).

Bioavailability
All subjects in the clinical programme described below were long-term intravenous or inhaled diacetylmorphine drug abusers. In a pilot clinical pharmacological study (two times five patients), the commonly used street method of ‘chasing the dragon’ was more effective at delivering diacetylmorphine via inhalation than a more clinical approach using a specifically designed heating device. Extent of exposure (Area Under the Curve (AUC)) in plasma when using the heating device compared to chasing was up to 80% and 73% lower for diacetylmorphine and 6-monoacetylmorphine respectively. Recovery rates of morphine in urine, expressed as percentage of diacetylmorphine dose administered, were in the range of 38 – 48%. In addition, subjects preferred the ‘chasing the dragon’ method over the use of the heating device. Therefore, the ‘chasing the dragon’ method was used in the clinical programme. The method ‘chasing the dragon’ works as follows; ‘Place the [diacetylmorphine] powder on a piece of aluminium foil and heat it carefully with a cigarette lighter to melt and vaporize it; inhale the arising fumes through a suitable straw or tube. Stop heating the medication in between inhalations, move the melted substance around on the aluminium foil and be careful not to overheat it, to avoid charring and burning.’

The second and major clinical pharmacology study used a parallel group design comparing intravenous versus inhaled diacetylmorphine, in 11 respectively 9 evaluable patients (Table PK 1). Although a

crossover design is preferred, the design is acceptable in view of long term diacetylmorphine users who were either accustomed to inhaling/chasing versus injecting diacetylmorphine. Bioavailability of inhaled diacetylmorphine ranged from 44% to 52% depending on the analyte, i.e. morphine in urine or diacetylmorphine plasma data, and whether a non-compartmental or population pharmacokinetic (PK) model was used. Diacetylmorphine reached maximum plasma concentrations at 2.2 and 10 minutes after intravenous and inhaled administration, respectively. The active 6-monoacetylmorphine (6MAM), morphine and morphine-6-glucuronide (M6G) and inactive morphine-3-glucuronide (M3G) metabolites appear to a clinically significant extent rapidly thereafter (within 30 minutes) (Figure PK 1). Variation in diacetylmorphine maximum plasma concentration (C_{max}) was most likely explained by rapidly changing plasma levels and limited number of sampling times. Interpretation of data is hampered by different steady-state doses administered in the second study. A dose proportional increase in diacetylmorphine levels was observed for injected diacetylmorphine from 300 to 450 mg. For other dose levels and inhaled diacetylmorphine dose-proportionality could not be shown. However, subjects tolerated 50% dose increases from individual steady state doses.

Table PK 1 Comparison of diacetylmorphine HCl PK parameters after intravenous bolus injection and inhalation ('chasing the dragon') in opioid addicted subjects

IV bolus injection						
Dose Level	Statistic	Dose (mg)	t_{max} (min)	Cmax/D (ng/mL/mg)	$AUC_{0-\infty}$/D (h*µg/L/mg)	Cl/F (L/h)
Maintenance	Mean	287.7	2.2	11.6	1.32	875
	CV%			45	40	40
inhalation						
Dose Level	Statistic	Dose (mg)	t_{max} (min)	Cmax/D (ng.mL/mg)	$AUC_{0-\infty}$/D (h*µg/L/mg	Cl/F (L/h)
Maintenance	Mean	283.3	10.1	2.57	0.632	1989
	CV%			56	53	53

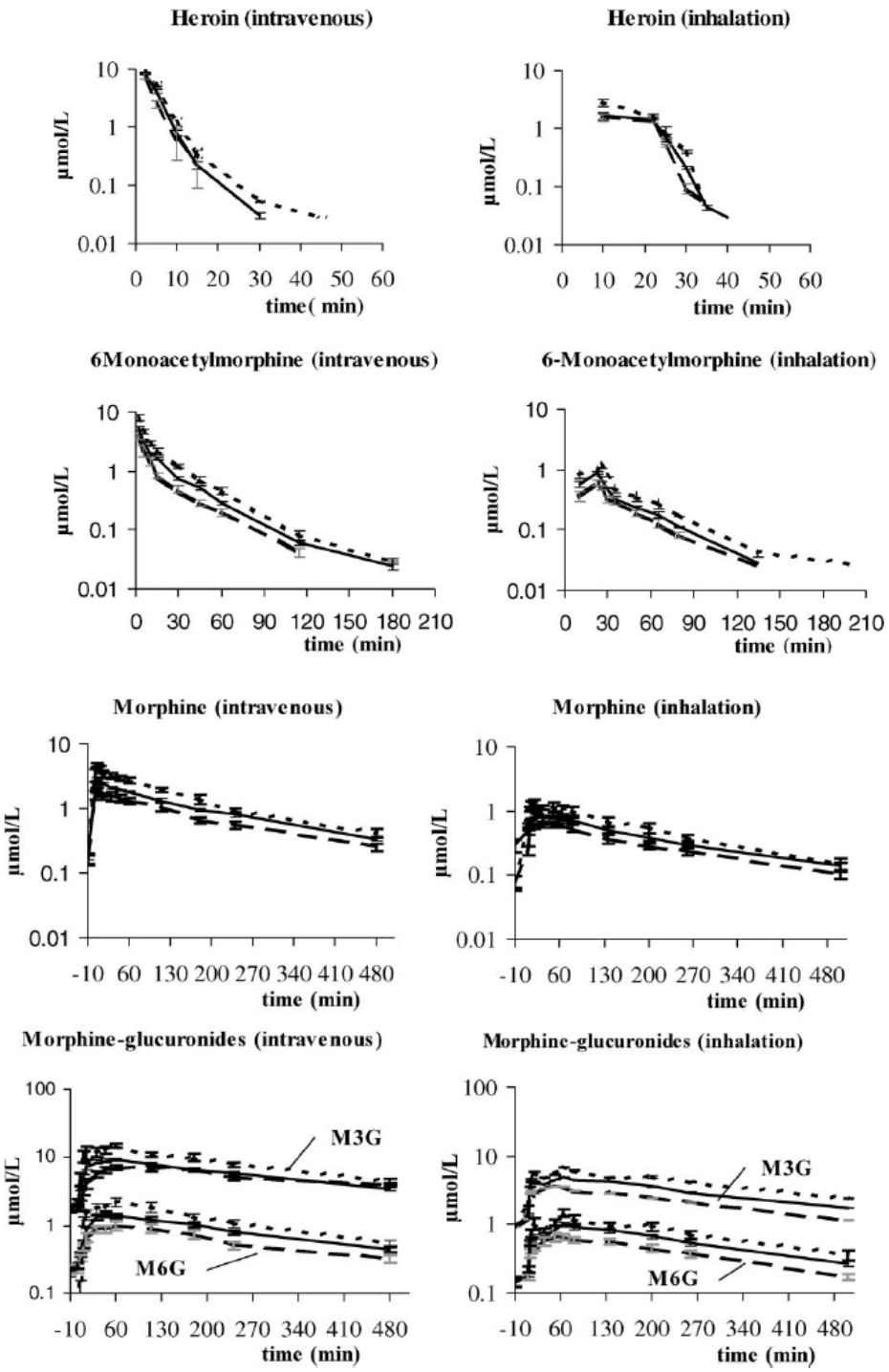

Figure PK 1. Mean plasma concentrations (with standard error) of diacetylmorphine (heroin), 6-monoacetylmorphine (6MAM), morphine, morphine-glucuronides at three dose levels after intravenous diacetylmorphine administration and after diacetylmorphine inhalation. The intravenous injection ended at t=0, while the inhalation session started at t=0. At t=10 min, 40% of the diacetylmorphine dose is inhaled, at t=20 min, 100% of the diacetylmorphine dose is inhaled. In reality, inhalation times varied between subjects, but for clarity all scheduled measurements are depicted independently of the individual inhalation time. —— steady state diacetylmorphine dose, – – – diacetylmorphine dose reduction - 33%, - - - diacetylmorphine dose increment + 50%

Distribution
Diacetylmorphine has a volume of distribution (Vd) in the range of 60 to 100L and has a clinically insignificant protein binding (20 to 40%).

Metabolism
The metabolism of diacetylmorphine is well-known from the literature; its main metabolites are formed within minutes after administration. Diacetylmorphine has a terminal half-life of approximately 3 minutes. Except for morphine-3-glucuronide (M3G), all metabolites contribute to the opioid activity of diacetylmorphine. M3G may be associated with diacetylmorphine neuro-excitatory adverse effects. The active metabolites, 6-monoacetylmorphine (6MAM) and morphine, are formed by hydrolysis, to a large extent extrahepatically, which is mediated by esterases in human plasma. This leads to a diacetylmorphine clearance > 500 L/h. Diacetylmorphine is for 70% excreted in urine as 6MAM, morphine and the morphine-glucuronides; M3G and morphine-6-glucuronide (M6G), with respective terminal half-lives of approximately 22, 180 and 280 minutes. Diacetylmorphine metabolism is therefore acceptably elucidated. The lack of unexpected metabolites formed as a result of uncontrolled contaminations from illicitly-acquired diacetylmorphine is a clear advantage for diacetylmorphine as a registered medicinal product. Despite the short terminal half-life of diacetylmorphine and its metabolites, patients have generally got accustomed to a twice daily dosing regimen. Accumulation of diacetylmorphine and active metabolites is therefore not expected to occur in the intended patient population. The impact of genetic polymorphism that may affect esterase, glucuronidation, P-glycoprotein (P-gp) and organic anion-transporters (OATP) expression was discussed briefly. Based on current scientific knowledge polymorphism of 5'-diphosphate-glucuronyltransferases (UGT) is not expected to cause clinically significant differences in morphine glucuronidation.

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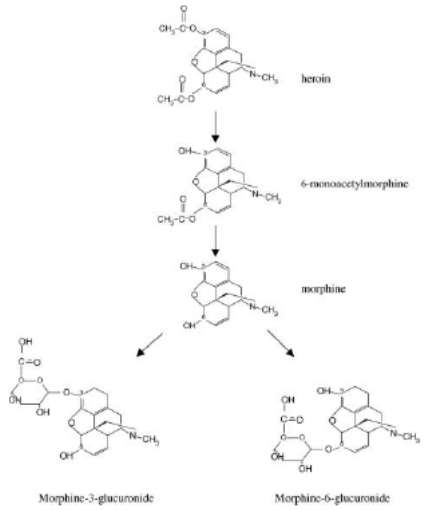

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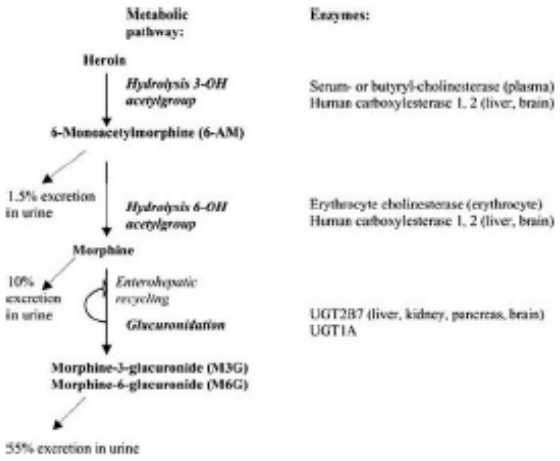

Figure PK 2. Metabolism of heroin (diacetylmorphine) and its major metabolites. Heroin is hydrolysed to 6-monoacetylmorphine and morphine. Glucuronides are conjugated to the 3' or 6' position of the phenantrene ring.
***A*:** taken from Rook et al, *Pharmacokinetics and Pharmacodynamics of High Doses of Pharmaceutically Prepared Heroin, by Intravenous or by Inhalation Route in Opioid-Dependent Patients*, Basic & Clinical Pharmacology & Toxicology 2006, 98, 86–9
***B*:** taken from Rook et al, *Pharmacokinetics and Pharmacokinetic Variability of Heroin and its Metabolites: Review of the Literature*, Current Clinical Pharmacology, 2006*, 1,* 109-118

The indication of the product concerns maintenance therapy for chronic diacetylmorphine users in addition to methadone therapy. Patients must be dosed to their individual needs, which will depend on their individual steady state dose of diacetylmorphine; therefore, assessment of repeated dosing on

accumulation of diacetylmorphine and its active metabolites seems to be less relevant. It should however be realised that in the intended patient population, additional doses may be taken outside the treatment programme. In that case, a clinically relevant accumulation may occur of the metabolites with a longer half-life affecting efficacy and safety. Variability in PK parameters is introduced by a patient's physiology, inhalation or chasing techniques and possibly by limitations of the sampling procedure due to the short half-life of diacetylmorphine. The observed variability is moderate and will most likely not play a major role in the maintenance dose required in this population of long-term diacetylmorphine users.

Special patient populations
Elderly, pediatric and race groups have not been investigated separately. Use in paediatric populations seems unlikely, unwanted and is not foreseen. Therefore, a lack of studies in this population is acceptable and use in children has been contraindicated. Since there is a large metabolic reserve in the elderly for the main metabolic processes, hydrolysis and glucuronidation, a large effect on diacetylmorphine pharmacokinetics is not expected. In view of the stable patient population (currently approx. 40 years old) and the medically supervised dosing, the effects of older age can thus probably be managed in the treatment programme. Interethnic differences have been observed in diacetylmorphine PK characteristics. However, no clear PK/PD relationship has been established and again is complicated by the presence of different active and non-active or even antagonistic metabolites. Nevertheless, in this specific group of experienced diacetylmorphine users the lack of PK/PD data is probably of minor clinical relevance.

Hepatic impairment is not expected to have a large impact on diacetylmorphine and its metabolites PK. A large extrahepatic metabolic reserve exists for hydrolysis and glucuronidation capability is preserved long in patients with hepatic impairment. Therefore, only in patients with severe hepatic impairment morphine metabolism is expected to be affected. Renal impairment is expected to have an impact on the diacetylmorphine metabolite pharmacokinetics. The data showed a limited impact of impaired renal function on diacetylmorphine plasma levels. Interpretation is complicated as all studies lack patients with considerable renal impairment (CrCl < 60 mL/min) and the presence and change in balance of active and non-active metabolites. A general warning regarding patients with renal impairment is considered acceptable in the setting of observed treatment in these experienced diacetylmorphine users.

A well-validated sequential two-compartmental population PK model was developed for diacetylmorphine, 6-monoacetylmorphine (6MAM) and morphine, the morphine glucuronides were fitted separately in one-compartmental models. Complete PK data was available for 20 patients from the second clinical pharmacology study and sparse sampling PK data from 84 patients participating in the clinical trials programme. Covariates studied were bodyweight, body mass index (BMI), gender and creatinine clearance and the influence of benzodiazepines and alcohol. The data are generally consistent with non-compartmental data, although a possible effect of renal function and bodyweight on diacetylmorphine PK was not confirmed. A clinically insignificant 13% lower 6MAM excretion was observed in cocaine users. Concomitant drug use was based on self-reported use in the clinical trial, which may have led to unreliable data in this patient group.

Drug-drug interactions (see Table PK 2)
The interaction potential of diacetylmorphine and its metabolites can be influenced by drugs affecting hydrolysis of diacetylmorphine and 6MAM, and drugs interfering with glucuronidation of morphine. Little is known on drugs interacting with hydrolysis. Ethanol has been shown to inhibit hydrolysis and affect glucuronidation of the morphine metabolite. Ethanol consumption was associated with overdosing in observational studies. Absorption of diacetylmorphine and morphine (in the entero-hepatic cycle) may be affected by P-gp and OATP. Inhibition of (drug-)transporters may have an impact on diacetylmorphine metabolite Blood Brain Barrier (BBB) distribution. Genetic polymorphism may affect these metabolism and absorption pathways, but to current scientific knowledge the extent seems to be limited. While a good mechanistic overview is given based on the public literature, diacetylmorphine's drug-drug interaction profile is only investigated in the population PK study. A limited effect of cocaine on diacetylmorphine PK could be demonstrated, while a theoretical inhibitory effect of benzodiazepines on glucuronidation could not be demonstrated. Clinical implications may be difficult to predict as inhibition of metabolism may lead to both prolonged action of diacetylmorphine or 6MAM, but also to lower concentrations of the very potent morphine-6-glucuronide for example.

Various mainly psychoactive drugs are frequently used concomitantly with diacetylmorphine, such as benzodiazepines. Respiratory depression is a safety risk and therefore a warning is incorporated in the

Summary of Product Characteristics (SPC). Further drug-drug interaction studies to elaborate PK and PD effects are difficult to perform in this specific patient population, while it is unethical to administer diacetylmorphine to healthy volunteers. Therefore, in view of the controlled clinical setting of diacetylmorphine administration, no further interaction studies have been requested.

Table PK 2. Drug-drug interactions of diacetylmorphine and its metabolites*

Co-medication	Interaction	Type of Study, Results		Clinical Relevance	Reference
Hydrolysis of heroin and 6-monoacetylmorphine (6-AM)					
Cocaine	Inhibition	*In vitro*	Competitive inhibition	Unknown	[77]
Ethanol	Inhibition	*Post-mortem*	In presence of ethanol 6-AM levels ↑	Enhanced risk for overdose	[82]
Glucuronidation to morphine 3-glucuronide (M3G) and morphine-6-glucuronide (M6G)					
Acetaminophen (paracetamol)	Induction	*In vivo*	Observational study morphine treated patients	Unknown	[88]
Benzodiazepines	Inhibition	*In vitro* *In vivo*	Competitive inhibition M3G formation relatively more inhibited by oxazepam. Trend for ↓ M3G/morphine serum ratio in morphine treated patients	Unknown Unknown	[84-88,119]
Chloramphenicol	Inhibition	*In vitro* *In vivo*	Competitive inhibition Rodents, extreme doses chloramphenicol, AUC morphine ↑	Unknown	[89,90]
Ethanol	Inhibition	*In vitro*	Dose dependent	Unknown	[83]
Ranitidine	Inhibition	*In vitro* *In vivo*	M6G forming relatively spared Healthy volunteers	Opioid effect ↑	[94,120]
Amitriptyline, nortriptyline, fluoxetine	Inhibition	*In vitro*	Competitive + non-competitive	Unknown	[91]
Zidovudine	Inhibition	*In vitro*		Clinical morphine sparing effect	[92]
Transporting enzymes (morphine substrates)					
Quinidine	P-gp blocker	*In vivo*	Healthy volunteers, oral morphine: AUC morphine ↑	iv morphine: insign. PK/PD interaction effect	[100,101]
Valspodar	P-gp blocker	*In vivo*	Healthy volunteers, iv morphine: AUC M3G ↑	Insign. PD effects	[102]
Rifampin	P-gp induction	*In vitro* *In vivo*	Healthy volunteers Double-blind crossing over Bioavailability oral morphine ↓	Analgesic effect ↓	[72,103]
Probenecid	OATP blocker	*In vitro* *In vivo*	Rodents, antinociception ↑	Unknown	[75,104]

OATP= organic anion transporters, P-gp= P-glycoprotein, AUC= area under the curve.

* **Table taken from** Rook et al, *Pharmacokinetics and Pharmacokinetic Variability of Heroin and its Metabolites: Review of the Literature*, Current Clinical Pharmacology, 2006*, 1,* 109-118.

Overall conclusion on Clinical Pharmacology

The submitted PK/PD dossier was considered acceptable for a marketing authorisation considering that the intended patient population consists of experienced diacetylmorphine users on a stable, individualised diacetylmorphine dose. The short half-life of diacetylmorphine, the presence of active and non-active metabolites, and the ethical consequences of performing studies in healthy volunteers limited the scope of the clinical pharmacology programme.

Clinical Efficacy

The programme initiated to investigate the benefits and risks of co-prescribed inhaled and intravenous heroin (diacetylmorphine base and diacetylmorphine hydrochloride, respectively) consisted of two pivotal active-controlled studies: CS-1-IV and CS-2-IH. Patients who responded to co-prescribed diacetylmorphine in the comparative phase of these studies could, on a compassionate basis, receive diacetylmorphine beyond the protocol period and were assessed thereafter on a yearly basis (extension study CS-3-1/2-FU/2000). Following the outcome of the two pivotal comparative studies, a third open 12-month study of injectable or inhalable diacetylmorphine co-prescription was initiated early in 2003 (study CS-4-V1/2003). A brief overview of the clinical programme is provided in the table below.

Table E1. Overview of the Diacetylmorphine co-prescription programme

	Intravenous co-prescription (n)	**Inhaled co-prescription (n)**
Pivotal randomised, open, methadone controlled studies, 12 months.	180 randomised (study **CS-1-IV**)	390 randomised (study **CS-2-IH**)
Extension > 18 months. (study **CS-3-1/2FU/2000**)	from above population 42 >2 years 33 >3 years	from above population 90 >2 years 63 >3 years
Open, uncontrolled intravenous or inhaled diacetylmorphine, 12 month. (study **CS-4-V1/2003**)	39	100

Design and Methodology

Pivotal studies CS-1-IV and CS-2-IH were open-label, randomised, reference-controlled clinical studies in chronic treatment resistant diacetylmorphine addicts. Treatment resistance was defined by a documented history of diacetylmorphine dependence for at least 5 years, unsuccessful treatment in a regularly attended methadone maintenance programme, (near) daily illicit diacetylmorphine usage as well as a poor mental health and/or poor physical health and/or poor social functioning. In the comparative phase of these studies (ie., study phase II), patients were randomised to receive either methadone monotherapy or methadone plus diacetylmorphine co-prescription for 12 months (groups A and B, respectively). In the diacetylmorphine inhalation study CS-2-IH, an additional comparative group was included that received oral methadone for the first 6 months followed by prescribed diacetylmorphine in combination with methadone maintenance from month 6 to 12 (group C). Early in study phase III, a 2-month diacetylmorphine withdrawal period was planned for those patients who received diacetylmorphine co-prescription during study phase II. Further details on the design of studies CS-2-IH and CS-1-IV are provided in the two tables below.

Table E2. Design study CS-2-IH

Treatment group	Phase I (4-8 weeks) qualification and randomisation	Phase II (12 months) treatment comparison		Phase III (6 months) follow-up
		IIa (6 months)	IIb (6 months)	
A	methadone	methadone		methadone + diacetylmorphine *
B	methadone	methadone + diacetylmorphine		most appropriate care **
C	methadone	methadone	methadone + diacetylmorphine	most appropriate care **

* At the end of phase III, the co-prescription of diacetylmorphine was withdrawn; two months later, these patients had their final assessments. ** No co-prescribed diacetylmorphine for the first two months; after that only co-prescribed diacetylmorphine on medical indication and on an individual basis.

Table E3. Design study CS-1-IV

Treatment group	Phase I (4-8 weeks) qualification and randomization	Phase II (12 months) treatment comparison	Phase III (6 months) follow-up
A	methadone	methadone	methadone + IV diacetylmorphine *
B	methadone	methadone + IV diacetylmorphine	most appropriate care **

IV; intravenous. * At the end of phase III, the co-prescription of diacetylmorphine was withdrawn; two months later, these patients had their final assessments. ** No co-prescribed diacetylmorphine for the first two months; after that only co-prescribed diacetylmorphine on medical indication and on an individual basis.

As expected, patients who were randomised to methadone monotherapy during study phase II (group A) obtained illicit diacetylmorphine from other resources. All patients concomitantly received a standard offer of psychosocial interventions. The studies were unique in a sense that both study drugs (methadone and illicit diacetylmorphine) were already used by the included study population on a (nearly) daily basis. Notable changes for patients enrolled and allocated to diacetylmorphine co-prescription were the quality of the diacetylmorphine (pharmaceutical-grade versus unpredictable street quality), the availability of the diacetylmorphine (supplied on daily basis at no cost versus nearly daily usage with dependency on paid drug dealers), and more frequent visits to treatment units for diacetylmorphine administration allowing intensive contact with trained, experienced personnel (up to three times daily versus up to once daily in the methadone maintenance programme). The absence of a need to dispense methadone up to three times daily at treatment units made the direct comparison against diacetylmorphine co-prescription less clear-cut due to the difference in contact frequency. In the pivotal studies, treatment response was defined as a dichotomous, multi-domain outcome index containing the aspects physical health, mental status and social functioning. In detail, efficacy was assessed with respect to outcome on the domains of (1) somatic status, (2) psychiatric status and (3) social integration and social functioning. Patients were considered as responders if they showed at least marked (40%) improvement on the outcome assessment compared to the situation at baseline in at least one of the domains in which they functioned poorly at the start of the study (i.e. on the basis of which they were included at baseline), without a substantial deterioration in the other outcome domains and without substantial increase in illicit drug use.

Main results

In study CS-1-IV, a total of 180 patients were randomised to treatment, while 390 patients were randomized to treatment in CS-2-IH. Within the significant methodological limitations posed by the open-label design and the subjective nature of the validated outcome measures, the two pivotal randomized studies indicated that a poor mental, physical and/or social status of treatment-resistant diacetylmorphine addicts could be improved by the daily distribution of co-prescribed inhaled or intravenous diacetylmorphine as compared to methadone ‘monotherapy’ (i.e. probably with concomitant [near-daily]

use of illegal diacetylmorphine from other sources). A larger proportion of treatment responders was observed in the group receiving 12 months of inhaled diacetylmorphine co-prescription (group B) versus the group receiving methadone 'monotherapy' (group A) in study CS-2-IH; 48% versus 25% respectively. Controlling for differences in response rate between the treatment sites, the difference of 23% corresponded with an adjusted odds-ratio for treatment group of 2.77 (95% - CI: 1.63 - 4.71; p = 0.0002). Similarly, a larger proportion of responders was observed in study CS-1-IV in the group receiving intravenous diacetylmorphine co-prescription (group B) compared to the group receiving methadone 'monotherapy' (group A); 57% versus 32% respectively. Controlling for differences in response rate between the treatment sites, the difference of 25% corresponded with an adjusted odds-ratio for treatment group of 2.99 (95% - CI: 1.58 - 5.65; p = 0.0008) in study CS-1-IV. Importantly, the observed improvement was neither at the expense of a substantial deterioration in the remaining outcome domain nor was it accompanied by a substantial increase in the use of cocaine or amphetamines. Results regarding treatment group C in study CS-2-IH and secondary analyses in studies CS-2-IH and CS-1-IV supported these findings.

As previously noted, the difference between the treatment arms with respect to the contact frequency at treatment units has the potential to impact on the observed treatment effect. Due to its addictive nature and required dosing regimen, diacetylmorphine co-prescription enforced a higher contact frequency at treatment units as compared to methadone 'monotherapy'. However, it is acknowledged that no therapeutic alternatives exist requiring such a high administration frequency that would be expected to result in the observed high level of compliance in these problematic diacetylmorphine addicted subjects. Thus, even if a higher contact frequency would be an important (co-)driver of therapeutic success, it is noted that apparently there are no other established ways to achieve this in these particular patients. Nevertheless, the observation of a substantial deterioration among diacetylmorphine treatment responders who continued their frequent treatment unit visits during diacetylmorphine withdrawal in the early part of study phase III, indicated that visit frequency did not largely account for the difference in treatment response between the co-prescription and methadone 'monotherapy' group.

The supplemental data from the extension study (study CS-3-1/2-FU/2000) and the third open 12-month study of injectable or inhalable diacetylmorphine co-prescription (study CS-4-V1/2003) supported the findings obtained in pivotal studies CS-1-IV and CS-2-IH, and indicated that clinical efficacy was maintained during long-term co-prescription. Overall, the data indicated a significant benefit for patients through the co-prescription of either intravenous or inhaled diacetylmorphine in selected patients with long-standing diacetylmorphine dependency.

Clinical Safety

In view of the pharmaceutical-grade quality heroin (diacetylmorphine base or -hydrochloride), daily co-prescription would not be expected to pose a major further safety risk compared to an ongoing (nearly) daily use of street-quality illegal diacetylmorphine in heroin addicted patients without co-prescription. An overview of the numbers of patients enrolled in the pivotal studies is provided below.

Table S1. Patients included in safety evaluations (Study CS-2-IH)

	GROUP A (methadone monotherapy)		**GROUP B (diacetylmorphine co-prescription)**		**GROUP C (methadone > diacetylmorphine)**		**TOTAL**	
	RANDOM.	ITT POP.	RANDOM.	ITT POP.	RANDOM.	ITT POP.	RANDOM	ITT POP.
Total	142	139	122	117	126	119	390	375

Random.; randomized. ITT pop.; intention to treat population.

Table S2. Patients included in safety evaluations (Study CS-1-IV)

	Group A (methadone monotherapy)		**Group B (diacetylmorphine co-prescription)**		**Total**	
	Randomized	ITT Pop.	Randomized	ITT Pop.	Randomized	ITT Pop.
Total	101	98	79	76	180	174

ITT pop.; intention to treat population.

Pivotal study CS-2-IH

Regarding common adverse events observed in the direct comparative, reference controlled phase of the diacetylmorphine inhalation study (CS-2-IH phase II, 0-12 months), infections were frequently reported in all three treatment groups. The incidences were generally comparable across treatment groups at rates between 30-36%. The incidence of respiratory adverse events was more than three times greater in the co-prescription groups versus the methadone 'monotherapy' group (21-25% versus 7% respectively), which was driven by the adverse events cough and (exacerbations of) chronic obstructive airway disease. Although less common, incidences of psychiatric and nervous system adverse events in the co-prescription groups were approximately twofold higher compared to the methadone 'monotherapy' group. The table below shows a detailed overview of the incidence and number of patients reporting adverse events within the system organ class (SOC) categories, where there are more than 3 reports in each system organ class.

Table S3. Percentage of Patients Reporting Adverse Events (AE) / SOC in month 0-12 (study CS-2-IH)

SOC	Patients (Pts) Reporting AE/SOC						
Infections	% Pts (n)	Influenza % Pts (n)	Pneumonia % Pts (n)	RTI % Pts (n)	Bronchitis % Pts (n)	Abscess % Pts (n)	UTI %Pts(N)
A.Methadone	30.0 (42)	10.7 (15)	7.9 (11)	5.6 (8)	2.8 (4)	0.7 (1)	0.7 (1)
B. Heroin	36.2 (46)	11.0 (14)	10.2 (13)	4.1 (5)	2.5 (3)	1.6 (2)	3.1 (4)
C. Heroin > Meth.	35.8 (44)	8.9 (11)	4.1 (5)	10.1 (12)	6.7 (8)	4.2 (5)	1.6 (2)
Respiratory		Cough	COAD + Exacerbation	Dyspnoea			-
A.Methadone	7.1 (10)	1.4 (2)	2.2 (3)	1.4 (2)	-	-	-
B. Heroin	25.2 (32)	15.0 (19)	10.6 (13)	4.7 (6)			
C. Heroin > Meth.	21.1 (26)	10.6 (13)	5.9 (7)	4.1 (5)			
Gastric		Nausea	Vomiting	Abdom. Pain	-	-	-
A.Methadone	12.9 (18)	2.9 (4)	2.1 (3)	2.1 (3)	-		
B. Heroin	22.8 (29)	11.0 (14)	7.1 (9)	3.1 (4)			
C. Heroin > Meth.	10.6 (13)	1.6 (2)	2.4 (3)	0.8 (1)			
General	% Pts (n)	Influenza-like sympt.	Chest discomfort	Fatigue	-	-	-
A.Methadone	12.1 (17)	2.9 (4)	0 (0)	2.1 (3)			
B. Heroin	21.3 (27)	6.3 (8)	6.3 (8)	3.1 (4)	-	-	-
C. Heroin > Meth.	17.1 (21)	4.1 (5)	5.7 (7)	0 (0)			

Psychiatric		Psychotic event	Emotional distress	-	-	-	-
A.Methadone	8.6 (12)	1.4 (2)	0 (0)				
B. Heroin	17.3 (22)	4.7 (6)	0 (0)	-	-	-	-
C. Heroin > Meth.	13.0 (16)	0.8 (1)	3.3 (4)				
Skin	% Pts (n)	Skin Ulcer	-	-	-	-	-
A.Methadone	4.3 (6)	2.9 (4)					
B. Heroin	15.7 (20)	2.4 (3)	-	-	-	-	-
C. Heroin > Meth.	6.5 (8)	0.8 (1)					
Injury/Poisoning	% Pts (n)	Injury	Contusion	Overdose	-	-	-
A.Methadone	14.3 (20)	2.1 (3)	2.9 (4)	2.1 (3)			
B. Heroin	13.4 (17)	2.4 (3)	2.4 (3)	1.6 (2)	-	-	-
C. Heroin > Meth.	18.7 (23)	4.1 (5)	4.1 (5)	2.4 (3)			
Nervous Sys.		Epilepsy	-	-	-	-	-
A.Methadone	5.7 (8)	2.9 (4)					
B. Heroin	12.6 (16)	2.4 (3)	-	-	-	-	-
C. Heroin > Meth.	14.6 (18)	3.3 (4)					

* RTI= respiratory tract infection (incorporates upper and lower). COAD: chronic obstructive airway disease. UTI: urinary tract infection. Abdom; abdominal.

In general, the rates of common adverse events were higher in the 12-month diacetylmorphine co-prescription group compared to the methadone 'monotherapy' and 6-month co-prescription group, especially regarding respiratory complaints. Although the rate on psychotic events reported as common adverse event was lower in the methadone 'monotherapy' group compared to the 12 month co-prescription group, comparable rates on psychotic events reported as serious adverse events were observed in these treatment groups. Overdoses and seizures occurred with comparable incidences across treatment groups. One death occurred due to a cardiac arrest in a patient receiving methadone 'monotherapy', while no deaths occurred in the diacetylmorphine co-prescription groups in phase II of the study. The overall incidence of serious adverse events was comparable across treatment groups at rates between 8-12%. Frequently reported serious adverse events concerned psychosis and respiratory disorders in these patients. A noteworthy finding concerning blood biochemistry related to a tendency to anemia at baseline, which may be related to inadequate nutrition, as reflected by low mean body weight. The high proportion of patients with elevated leukocyte levels was probably a refection of the high infection rate and the high prevalence of HIV/hepatic infections in these patients. Regarding discontinuations, the main causes for exclusion from the analysis in co-prescribed patients who completed phase II of the study were failure to take up the diacetylmorphine treatment offer (study drug never taken) and subject refusal after starting study drug, both of which may have been related to the novel requirements for daily attendance at the treatment units and supervised diacetylmorphine administration. Sanctioned banning from the study for unacceptable behaviour was also observed. Safety issues (i.e. occurrence of common adverse events, serious adverse events and deaths) did not show to be important factors in the difference between the methadone 'monotherapy' and co-prescription groups with respect to the number of exclusions from the phase II completer analysis.

Pivotal study CS-1-IV

Regarding common adverse events observed in the reference controlled phase of the intravenous study (CS-1-IV phase II, 0-12 months), infections were frequently reported The incidences were similar in the co-presciption and methadone ‘monotherapy’ groups at rates between 36-37%, which is in agreement with the pivotal inhalation study CS-2-IH. As would be expected, the incidence for the respiratory system adverse events was lower in co-prescription group of the intravenous compared to the inhalation study, but still increased versus the reference control group (10% versus 5%, respectively). The incidences of psychiatric, nervous, and skin complaints were approximately three times higher compared to the methadone ‘monotherapy’ group. These increased rates on skin complaints may be related to the intravenous diacetylmorphine administration route in this study. Regarding the psychiatric adverse events, the incidence of psychosis was higher in the co-prescription compared to the methadone ‘monotherapy’ group (2.5% versus 1%, respectively), but the former rate was substantially lower compared to the rate in the co-prescription group of the pivotal inhalation study (10%). Unlike the inhalation study data, the intravenous study showed increased rates on headache, migraine and paraesthesia versus active control (4% versus 1%, respectively). The table below shows a detailed overview of the incidence and number of patients reporting adverse events within the system organ class categories, where there are at least 3 reports in each system organ class (see next page).

Table S4. Adverse events with a frequency of ≥ 3 reports in the 12 months treatment period, by treatment group (CS-1-IV)

ORG. SYSTEM N= patients (Pts) assessed	AEs Reported ≥ 3 overall						
INFECTION	*% Pts* (N = *Pts*)	ABSCESS LIMB *% Pts* (N)	BRONCHITIS *% Pts (N)*	HERPES SIMPLEX *% Pts* (N)	INFLUENZA *% Pts* (N)	INJECT. SITE ABSCESS *% Pts* (N)	NASO/ PHARYNGITIS *% Pts* (N)
A. METHADONE	*36.0* *(36)*	5.0 (5)	4.0 (4.0)	1.0 (1)	9.0 (9)	4.0 (4.0)	5.0 (5)
B. HEROIN	*36.7* *(29)*	- (0)	- (0)	2.5 (2)	8.9 (7)	2.5 (2)	3.8 (3.0)
INFECTION		PNEUMONIA	RESP. TRACT	-	-	-	-
A. METHADONE	‘’	4.0 (4)	2.0 (2)	-	-	-	-
B. HEROIN	‘’	7.6 (6)	3.8 (3)	-	-	-	-
INJURY + POISONING		CONTUSION	Hand Fracture	INJURY	OVERDOSE	-	-
A. METHADONE	*16.0* *(16)*	4.0 (4)	3.0 (3)	1.0 (1)	3.0 (3)	-	-
B. HEROIN	*30.4* *(24)*	2.5 (2)	- (0)	3.8 (3)	8.9 (7)	-	-
GENERAL		CHEST PAIN	FATIGUE	INFLUENZA-LIKE	INJECT. SITE PRURITUS	MALAISE	PERIPHERAL OEDEMA
A METHADONE	*10.0* *(10)*	1.0 (1)	4.0 (0)	3.0 (3)	- (0)	1.0 (1)	1.0 (1)
B. HEROIN	*24.1* *(19)*	2.5 (2)	- (0)	7.6 (6)	3.8 (3)	2.5 (2.0)	3.8 (3)
NERVOUS		EPILEPSY	HEADACHE	MIGRAINE	PARAESTHESIA	-	-
A. METHADONE	*7.0* *(7)*	3.0 (3)	1.0 (1)	1.0 (1)	- (0)	-	-
B. HEROIN	*20.3* *(16)*	3.8 (3)	3.8 (3)	3.8 (3)	3.8 (3)	-	-
PSYCHIATRIC		ANXIETY	DEPRESSION	PARANOIA	PSYCHOTIC DISORDER	-	-
A. METHADONE	*7.0* *(7)*	- (0)	3.0 (3)	1.0 (1)	1.0 (1)	-	-
B. HEROIN	*20.3* *(16)*	5.1 (4)	2.5 (2)	3.8 (3)	2.5 (2)	-	-
SKIN		ECZEMA	PRURITIS	RASH	-	-	-
A. METHADONE	*5.0* *(5)*	1.0 (1)	- (0)	- (0)	-	-	-
B. HEROIN	*21.5* *(17)*	6.3 (5)	3.8 (3)	3.8 (3)	-	-	-
GASTRIC		NAUSEA	VOMITING	-	-	-	-
A. METHADONE	*6.0* *(6)*	1.0 (1)	2.0 (2)	-	-	-	-
B. HEROIN	*11.4* *(9)*	2.5 (2)	2.5 (2)	-	-	-	-
RESPIRATORY		DYSPNOEA	PRODUCT. COUGH	-	-	-	`-
A. METHADONE	*5.0* *(5)*	1.0 (1)	1.0 (1)	-	-	-	-
B. HEROIN	*10.1* *(8)*	2.5 (2)	3.8 (3)	-	-	-	-

Overall, in agreement with the pivotal inhalation study, these data from the pivotal intravenous study also showed that common adverse event rates were generally higher in the diacetylmorphine co-prescription group compared to reference control group. This might be related to a somewhat more frequent usage of diacetylmorphine in the co-prescription compared to the methadone 'monotherapy' group, despite a potential safety advantage resulting from the anticipated quality difference of the diacetylmorphine in the co-prescription compared to the methadone 'monotherapy' group (pharmaceutical- grade versus uncertain street-quality, respectively). Two deaths occurred during the 12 month study period, one in each treatment group. Thus, consistent with data from study CS-2-IH, these rates do not indicate an increased mortality with co-prescribed diacetylmorphine. The overall incidence of serious adverse events was comparable across treatment groups at rates between 7-11%. The nature of these serious adverse events was highly variable, and none of them was considered definitely related to study medication. In agreement with the pivotal inhalation study, blood biochemistry indicated an overall tendency to anemia already present at baseline, likely related to inadequate nutrition. There did not appear to be treatment-related differences in hematological or blood enzyme measures during the study. The pattern of discontinuations observed in study CS-1-IV was comparable to that observed in CS-2-IH.

Supportive studies CS-3-1/2-FU and CS-4-V1-2003

The omission of a reference control group in the open label extension study CS-3-1/2-FU limited the interpretation of the findings in this selected patient group of diacetylmorphine restarters. No deaths occurred under study medication in either treatment group. Serious adverse events of various causality occurred. No events of epileptic seizures or psychosis were noted, but one event of exacerbated chronic obstructive airway disease in the inhaling group was possibly related to study medication. No serious adverse events was assessed as having a definitive relationship to treatment. The absence of a reference control group also restricted the interpretation of safety findings in the non-randomised, open-label follow-up study CS-4-V1-2003. Consistent with previous pivotal studies, most adverse events were noted in the infection, nervous and respiratory system. The overall incidence of infections was comparable between the administration groups at rates between 26-30%. Again, the inhaled administration form was associated with higher rates on respiratory complaints related to airway obstruction, some of which were reported as serious adverse event. Epileptic seizures were more frequently observed with intravenous diacetylmorphine compared to the inhaled administration form (13% versus 3%, respectively). A similar proportion of patients experienced serious adverse events in both administration groups (13%), of which an event of vertrebral fracture, chest discomfort and an aggravated psychosis were considered possibly related to treatment. Three deaths occurred among these 139 patients over the first 12-month treatment period, none of which was considered definitely related to treatment.

Overall conclusion on safety

Overall, within the constraints of a limited number of patients treated in the medium-term (12-month) direct comparative phase of the pivotal studies, the data did not indicate an increased mortality rate in the diacetylmorphine co-prescription groups versus the methadone 'monotherapy' groups. No clinical outcome studies have been performed. The rates on common adverse events were generally higher with diacetylmorphine co-prescription in the pivotal studies, but the incidence of the most common adverse event (infections) was similar across treatment groups at a rate of 36%. Common adverse events which may be related to the use of intravenous or inhaled diacetylmorphine given concomitantly with oral methadone and occurring with an incidence above 5% were nausea and vomiting, influenza-like symptoms, psychiatric disorders (including anxiety, depression, and psychotic manifestations), respiratory symptoms (including cough, dyspnea, and asthma), eczema, and rash. A comparable serious adverse event profile appeared to be present across treatment groups in the pivotal studies. Important safety issues associated with the daily diacetylmorphine co-prescription are the potential for overdose and associated respiratory depression (in particular when additional illegal diacetylmorphine is used), exacerbations of chronic obstructive airway disease associated with the inhaled administration form, and the potential for psychosis or epileptic seizures in susceptible patients. These issues have been addressed in the product information and will also be implemented in the Risk Management Plan.

Risk Management Plan/Routine Pharmacovigilance

In line with the current legislation the marketing authorisation holder has provided a detailed risk management plan (RMP) which needs some further addition. The information included (also from the clinical data) has been taken in to account for the approved product information. In view of the controlled clinical setting in which the products are going to be used it was agreed that the marketing authorisation holder has committed to finalise the RMP, in agreement with the MEB, post authorisation.

The marketing authorisation holder has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The quality part of the dossier is of sufficient standard for authorisation. There are a small number of issues for which the marketing authorisation holder has provided commitments to address these issues post-authorisation.

The package of non-clinical safety studies presented in a literature overview is limited. The main reason for this is that the available studies were not performed as part of a formal drug development process as suggested by relevant guidelines, but they were performed as scientific investigations. This means that the studies cited do not comply with guidelines with regard to characterization of the test compound, duration of treatment, parameters measured, confirmation of level of exposure to the test compound and conduct according to Good Laboratory Practices. In addition, hardly any study was done in non-rodents, the route of administration was not always relevant to the intended human use of diacetylmorphine (intravenous or by inhalation). Specifically the lack of inhalatory toxicity studies on diacetylmorphine and caffeine can be seen as an omission. Also, carcinogenicity studies have not been performed with diacetylmorphine. Subsequently, the non-clinical (animal) risk assessment is incomplete and has mainly to be based on clinical experience. Yet, also taking note of the proposed indication (i.e. administration by patients already using diacetylmorphine) and the available clinical data, the MEB concluded that additional data from non-clinical studies would not alter the risk-benefit balance decisively.

The overall clinical benefit/risk assessment of diacetylmorphine co-prescription assumes that this treatment is only indicated in poorly functioning treatment-resistant patients with long-standing illegal heroin use, since diacetylmorphine co-prescription implicates ongoing dependence on diacetylmorphine. It is considered that diacetylmorphine co-prescription is associated with a clinically relevant and sustained improvement in personal and/or social functioning in selected diacetylmorphine-dependent patients, which offsets potential safety risks associated. A controlled distribution of diacetylmorphine through specialised treatment units is an essential requirement in this context.

Taking the overall data on quality, safety and efficacy data in to account the MEB considered that the use of diacetylmorphine base and diacetylmorphine hydrochloride (in the setting of co-prescription with methadone for a restricted indication and setting) has a satisfactory risk/benefit profile, and therefore granted a marketing authorisation.

The following clinical and pharmacovigilance commitments are provided by the marketing authorisation holder:

a) Clinical (powder for solution for injection): further substantiation of the 3 gram pack-size will be provided based on the average amount of diacetylmorfine HCl needed and historic data regarding the average amount discarded as soon as possible. If, based on these data, introduction of (a) smaller pack size(s) is deemed necessary by the MEB, such pack-sizes will be introduced.

b) Clinical: it will be discussed why Rook et al. in Basic & Clinical Pharmacology & Toxicology 2006 could evaluate the impact of bodyweight and renal function on metabolite data, while in the dossier it is stated that these parameters were not available.
c) Pharmacovigilance: lung function in relation to diacetylmorphine use by inhalation will be given special attention, the results of which will be reported in the regular PSUR cycle.
d) Pharmacovigilance: formation of neoplasms will be closely monitored and reported in the regular PSUR cycle.
e) Pharmacovigilance: use by patients with renal and liver impairment will be closely monitored and the results will be reported in the regular PSUR cycle.
f) Pharmacovigilance: adverse reactions which could be due to higher plasma levels as expected in a patient with polymedication will be closely monitored for possible interactions and this specific topic will be reported in the regular PSUR cycle.
g) Risk Management Plan (RMP): the RMP will be further discussed with and agreed upon by the MEB.
h) Summary of Product Characterisation (SPC): section 4.8 of the SPC will be brought into line with the current requirements with submission of the first PSUR.
i) Patient Leaflet: readability/user testing will be carried out as soon as possible and, when applicable, amendments to the PIL will be made.

Annexes:

Annex 01

SUMMARY OF PRODUCT CHARACTERISTICS
DIACETYLMORPHINE HCL 3 g

INTRAVENOUS / VIALS

1. NAME OF THE MEDICINAL PRODUCT

Diacetylmorfine HCl 3 g, powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of Diacetylmorfine HCl 3 g contains 3 grams of lyophilized diacetylmorphine hydrochloride (HCl). After reconstitution with 18 ml water for injection, 20 ml solution is obtained: 1 mL = 150 mg diacetylmorphine HCl.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

4. CLINICAL PARTICULARS

Important notice: Diacetylmorphine HCl should be self-administered under supervision only in specialized treatment units, approved for this purpose by the Dutch Ministry of Health, Welfare and Sports. The treatment units will provide clean, suitable facilities, as well as all requirements and medical assistance necessary for safe self-administration of diacetylmorphine hydrochloride.

4.1 Therapeutic indication
For use as adjunctive therapy in poorly functioning treatment-resistant patients with long-standing diacetylmorphine (heroin) dependency (DSM IV -TR 304.00), who administer by injection on a (near) daily basis, who have failed to respond to treatment in at least one regularly attended methadone maintenance programme, and who are currently treated with methadone (see section 5.1).

4.2 Posology and method of administration
Diacetylmorphine HCl should be used as an adjuvant intravenous therapy with oral methadone (minimum daily dose 30 mg), and can be administered up to three times a day. The maximum permitted daily dose is 1000 mg diacetylmorphine, with a maximum single dose of 400 mg diacetylmorphine. The dose of diacetylmorphine HCl should be titrated to the needs of the individual patient, taking into consideration the co-prescribed dose of methadone, the possibility of illegal heroin consumption or other illegal drug use, and health status. In clinical studies of up to 12 months, the mean daily dosages of co-prescribed diacetylmorphine HCl ranged between 434 – 520 mg divided over 2-3 administrations.

Caution should be exercised when administering diacetylmorphine to patients with moderate to severe renal impairment or severe hepatic impairment (see section 4.4).

Diacetylmorphine HCl is provided in vials containing 3 grams of lyophilized diacetylmorphine HCl per vial, to be reconstituted with 18 ml water for injections. The resulting solution (1 mL = 150 mg

diacetylmorphine HCl) is used to dispense the required dosages of diacetylmorphine in syringes, ready for intravenous self-administration by the patient. It is important to use sterile needles and syringes, to disinfect the injection site, and to use a safe technique and site for injection.

All (used and unused) syringes and needles should be returned to the supervising staff for destruction.

4.3 Contraindications
- Hypersensitivity to diacetylmorphine;
- Severe respiratory depression or cyanosis;
- Exacerbated chronic obstructive airway disease;
- Diacetylmorphine HCl has not been studied in children; use in children is therefore contraindicated.

4.4 Special warnings and precautions for use
- Diacetylmorphine should not be administered in patients with head injuries or raised intracranial pressure.
- Care should be exercised in treating patients with mild to moderate respiratory depression or obstructive airways disease, since diacetylmorphine may aggravate these conditions.
- Caution should be exercised in case of concurrent administration of monoamine oxidase inhibitors or within two weeks of discontinuation of treatment with these products.
- Caution should be exercised in treating patients with epilepsy or allergic skin reactions, and in elderly or debilitated patients.
- Caution should be exercised in treating patients with hepatic or renal impairment: accumulation of morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) may occur in patients with moderate to severe renal impairment, and metabolism of diacetylmorphine could be altered significantly in patients with severe hepatic impairment.
- Based on reports from published studies, diacetylmorphine can cause hypotension in patients who already have conditions or drug therapy that interfere with the ability to maintain normal blood pressure.
- Careful consideration should be given before treating patients with myxoedema or hypothyroidism, adrenocortical insufficiency, toxic psychoses, central nervous system depression, prostatic hypertrophy or urethral stricture, kyphoscoliosis, acute alcoholism and delirium tremens, severe inflammatory bowel disease and severe diarrhea.

4.5 Interaction with other medicinal products and other forms of interaction
In the intended patient population, concurrent use or abuse of other sedative, hypnotic, or stimulant drugs (including alcohol) should be taken into consideration when determining the dosage of diacetylmorphine HCl, as combination with these drugs can enhance the central depressant effects.

Caution should be exercised in treating patients on diacetylmorphine with oral or intravenous morphine, since both drugs share the same metabolic pathways and accumulation of metabolites could occur, especially in patients with hepatic or renal impairment.

Administration of drugs having anti-muscarinic activity (atropine and synthetic anticholinergics) may increase the risk of severe constipation and/or urinary retention.

It should be noted that there are no formal drug-drug interaction studies and that there is relatively little experience with long-term use of prescribed diacetylmorphine in combinations with other medications.

4.6 Pregnancy and lactation
There is little human data available regarding the use of diacetylmorphine during pregnancy.
In reports from the literature undesirable effects on animal offspring have been identified. Opiates cross the placenta. Administration of diacetylmorphine directly before parturition can result in respiratory

depression in the neonate. When opiates are taken throughout pregnancy and up to parturition withdrawal effects may occur in the neonate.
Use of diacetylmorphine in pregnancy is therefore not recommended, unless strictly necessary.

There is limited information on diacetylmorphine levels in breast milk.
In view of the possible respiratory depressive effects of diacetylmorphine on the neonate it is not advisable for patients using diacetylmorphine to breast-feed.

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. Given the pharmacological effects of diacetylmorphine including sedation, driving or operating machinery should be avoided.

4.8 Undesirable effects
The most serious hazards of diacetylmorphine HCl are respiratory depression and arrest, although circulatory depression, shock, and cardiac arrest can occur.

The most commonly observed adverse effects seen in studies in subjects with chronic treatment resistant diacetylmorphine dependency receiving diacetylmorphine for injection for 12 months or more were infections; the incidence (approximately 36%) was similar to patients using methadone-alone. The occurrence of infections may be a result of the lifestyle of these patients, however it cannot be excluded that the immunosuppressive properties of opiates also play a role.

Adverse events which may be related to the use of diacetylmorphine HCl given concomitantly with oral methadone and occurring with an incidence of >5% are: nausea and vomiting, influenza-like symptoms, occasional psychiatric disorders (including anxiety, panic attacks, panic disorder, paranoia, psychotic manifestations, and overdose incidents), respiratory symptoms (including cough, dyspnea, and asthma), eczema, and rash. The intravenous use of diacetylmorphine may increase the risk of epileptic seizures and psychoses in susceptible patients.

The very rare occurrence of leucoencephalopathy has been reported in the literature. Leucoencephalopathy has not been reported in the clinical studies as carried out in The Netherlands. Very rarely, brief spells of bradycardia have been observed immediately after intravenous injection of diacetylmorphine.

4.9 Overdose
The symptoms of serious overdosage are respiratory depression, stupor or coma, muscle flaccidity, cold clammy skin, constricted pupils, and occasionally bradycardia and hypotension, and seizures.

In case of acute overdose, patent airways should be re-established and assisted ventilation instituted if indicated. Supportive measures should be instituted in the case of circulatory shock and pulmonary edema.

Overdosage should be treated by careful administration of the opiate antagonist naloxone.
In physically diacetylmorphine-dependent patients, administration of naloxone may result in a reversal of opioid effects and precipitate an abstinence syndrome. Refer to prescribing information of naloxone for details of proper usage.

5. PHARMACOLOGICAL PROPERTIES

ATC Code: N02AA09 **Group: opioids**

5.1 Pharmacodynamic properties

Diacetylmorphine is a narcotic analgesic, a synthetic derivative of morphine, which acts mainly on the opioid receptors in the central nervous system and smooth muscle. Opioids, including diacetylmorphine, stimulate μ opioid receptors and affect a wide range of physiological systems. They produce analgesia, affect mood, modulate reward mechanisms in the brain as shown in behavioural models and alter respiratory, cardiovascular, gastrointestinal, and neuroendocrine function. It is obvious that in this context, particularly the latter four aspects are relevant in adjusting the dosages of diacetylmorphine.

All opioids including diacetylmorphine induce tolerance and physical dependence with repeated use.

The safety and efficacy of medically co-prescribed intravenous diacetylmorphine was evaluated in a total of 170 patients who were participating in methadone treatment programmes. The principal evidence of the safety and efficacy comes from a 12-month, randomized study of adjunctive diacetylmorphine prescription, compared to methadone maintenance alone, followed by a 6-month crossover period.

The study population consisted of poorly functioning, chronically treatment-resistant patients with a diagnosis of diacetylmorphine dependency (DSM IV – 304.00) lasting five years or more and who predominantly administered diacetylmorphine intravenously on a daily or near-daily basis. The participants had a long history of poly-drug use and unsatisfactory participation in addiction treatments, including long-term methadone maintenance programmes. Patients experienced treatment needs with regard to their physical health, psychiatric status, and/or social functioning.

Treatment response was defined as a dichotomous, multi-domain outcome index containing the aspects physical health, mental status and social functioning. Twelve months of diacetylmorphine co-prescription with oral methadone resulted in a significantly larger responder rate as compared to treatment with methadone alone (p=0.0008). Patients responding to diacetylmorphine co-prescription generally showed improvement on more than one domain.

The mean daily dosage of intravenously co-prescribed diacetylmorphine HCl in the controlled study (n= 79) given for 12 months, was 520.4 mg / day (SD+/- 207 mg) divided over 2-3 administrations per day. Is 520.4 mg niet te precies?In open studies following a similar protocol in which patients received intravenous diacetylmorphine for up to 12 months or more, the mean daily dosages ranged between 434 mg – 517 mg/day.

5.2 Pharmacokinetic properties

Absorption and distribution

After intravenous administration of diacetylmorphine HCl the maximum plasma concentration of diacetylmorphine is reached in 2 minutes. After entering into the bloodstream, diacetylmorphine distributes rapidly over the body and into the central nervous system.

Metabolism

Diacetylmorphine is rapidly hydrolyzed to 6-acetylmorphine and subsequently to morphine by esterases in plasma and tissue. Diacetylmorphine, 6-acetylmorphine and morphine all possess opioid agonistic activity. The observed C_{max} of diacetylmorphine is very variable, which is at least in part due to the rapidly changing plasma concentrations of diacetylmorphine that make exact determination of C_{max} difficult. Diacetylmorphine clearance is typically 500-2000 L/h, exceeding by far the combined renal and hepatic blood flow, due to the extra-hepatic hydrolysis. Plasma half-life values for diacetylmorphine, 6-

acetylmorphine and morphine are in the range of 3-5 min, 20 min, and 180 min, respectively, which is reflected in the much higher AUC of morphine compared to that of diacetylmorphine.
Morphine in turn ?? wat staat hier. in turn kan volgens mij vervallen. is glucuronidated to morphine-3-glucuronide and morphine-6-glucuronide in a ratio of about seven to one.

Elimination
The main route of elimination of diacetylmorphine is via the kidneys as 6-acetylmorphine (1.5%), morphine (10%) or morphine glucuronides (55%). Part of the morphine glucuronides is excreted into the bile and re-enters the circulation as morphine via enterohepatic recirculation.

Kinetic parameters after IV bolus injection of diacetylmorphine HCl in opioid addicted subjects**						
Dose Level	Statistic	Dose (mg)	t_{max} (min)	C_{max}/D (ng/mL/mg)	$AUC_{0-\infty}$/D (h*µg/L/mg)	Cl (L/h)
Maintenance	Mean	287.7	2.2	11.6	1.32	875
	CV%	-	-	45	40	40

** derived from study CCBH.KNL 40058 - reanalysis

Drug-drug interactions
Drugs interacting with the hydrolysis of diacetylmorphine and 6-acetylmorphine are expected to increase exposure. Ethanol enhances the risk of a diacetylmorphine overdose, possibly by inhibition of the hydrolysis.

Drugs inhibiting the glucuronidation of morphine may increase morphine levels, but may also prevent the formation of the potent opioid morphine-6-glucuronide. Although many classes of drugs have shown to inhibit glucuronidation in vitro, the clinical relevance is not clear.
Similarly, drugs inhibiting the extrusion pumps P-glycoprotein and Organic Anion Transporter Proteins (OATPs) may theoretically increase exposure.

5.3 Preclinical safety data
No specific preclinical toxicological studies have been performed which are designed to support a thorough, quantitative risk assessment of diacetylmorphine powder for inhalation vapour.
However, the information available from studies conducted mainly in rodents indicates that the main organ involved in the toxicity of diacetylmorphine is the central nervous system. At low doses, classic opiate-like effects appear, at higher doses sedation, respiratory depression, and convulsions are induced, leading to death at high doses.
The target organs of toxicity after repeated administration of diacetylmorphine appear to be: the testes, the skeletal muscle and the immune system.
Reproductive toxicity studies mainly show the potential of diacetylmorphine to adversely affect the development of the nervous system leading to structural, functional and behavioural deficits.
Diacetylmorphine has the potential to promote the occurrence of chromosomal damage but does not appear to be a direct genotoxic agent. Carcinogenicity studies have not been performed with diacetylmorphine, but its indirect effects on the chromosomes together with reduced immune competence of the patients may lead to an increased risk of developing tumors.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipient(s)
None.

6.2 Incompatibilities
None known.
Diacetylmorphine HCl should not be mixed with other drugs/substances.

6.3 Shelf-life
Unopened vial - 2 years
The opened and reconstituted product has a physical-chemical stability of 12 hours at ambient temperature when stored below 25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. Normally this would not be longer than 24 hours at 2 to 8°C, unless reconstitution has taken place undercontrolled and validated aseptic conditions.

6.4 Special precautions for storage
None

6.5 Nature and contents of container
Each pack contains ten 30-ml clear glass (type I) vials, closed with rubber stoppers and sealed with flip-off caps.

6.6 Instructions for use and handling
Diacetylmorphine HCl 3 g powder for solution for injection is intended for multiple use. After reconstitution, the resulting solution should be dispensed in syringes in patient-specific doses.

Suitable aseptic techniques should be used to reconstitute Diacetylmorphine HCl: sterile syringes, sterile needles, sterile gloves, sterile water for injections, and a clean, disinfected work surface should be used for reconstitution and preparation of patient-specific dosages.

The multiple dose container should not be given to patients.

Reconstitution of the lyophilised powder with 18 mL water for injections results in 20 mL of a clear, light yellow, slightly viscous 150 mg/mL solution of Diacetylmorphine HCl.

Any unused product or waste material (containing Diacetylmorphine HCl) should be disposed of in accordance with regulatory / legal requirements.

7. MARKETING AUTHORISATION HOLDER
Di-AcetylM BV
Postbus 90424
1006 BK Amsterdam
The Netherlands
Telephone: +31 (0)20 614 2641
Facsimile: +31 (0)20 614 0368
e-mail: info@di-acetylm.nl

8. MARKETING AUTHORISATION NUMBER(S)

Diacetylmorfine HCl 3 g, powder for solution for injection – RVG 33463

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT
December 14 2006

Annex 02

SUMMARY OF PRODUCT CHARACTERISTICS
DIACETYLMORPHINE BASE

POWDER FOR INHALATION VAPOUR / Sachets

1. NAME OF THE MEDICINAL PRODUCT

Is morfine bedoeld of morphine
Diacetylmorfine 75 mg, powder for inhalation vapour
Diacetylmorfine 100 mg, powder for inhalation vapour
Diacetylmorfine 150 mg, powder for inhalation vapour
Diacetylmorfine 200 mg, powder for inhalation vapour

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

All strengths of diacetylmorphine powder for inhalation vapour contain a mixture of 750 mg/g diacetylmorphine base and 250 mg/g caffeine anhydrate. Four strengths are available:
Diacetylmorphine 75 mg
Diacetylmorphine 100 mg
Diacetylmorphine 150 mg
Diacetylmorphine 200 mg

3. PHARMACEUTICAL FORM

Powder for inhalation vapour. Powder in sachet.

4. CLINICAL PARTICULARS

Important notice: Diacetylmorphine should be self-administered under supervision only in specialized treatment units, approved for this purpose by the Dutch Ministry of Health, Welfare and Sports. The treatment units will provide clean, suitable facilities, as well as all requirements and medical assistance necessary for safe self-administration of diacetylmorphine

4.1 Therapeutic Indication

For use as adjunctive therapy in poorly functioning treatment-resistant patients with long-standing diacetylmorphine (heroin) dependency (DSM IV -TR 304.00), who administer by inhalation on a (near) daily basis, who have failed to respond to treatment in at least one regularly attended methadone maintenance programme and who are currently treated with methadone (see section 5.1).

4.2 Posology and method of administration

Diacetylmorphine powder for inhalation vapour should be used as an adjuvant therapy together with oral methadone (minimum daily dosage 30 mg) and can be administered up to three times a day. The maximum permitted daily dose is 1000 mg diacetylmorphine, with a maximum single dose of 400 mg diacetylmorphine. The dose of diacetylmorphine should be titrated to the needs of the individual patient, taking into consideration the co-prescribed dose of methadone, the possibility of illegal heroin

consumption or other illegal drug use, and health status. In clinical studies of up to 12 months, the mean daily dosages of co-prescribed inhaled diacetylmorphine ranged between 485 – 617 mg divided over 2-3 administrations.
Caution should be exercised when administering diacetylmorphine to patients with moderate to severe renal impairment or severe hepatic impairment (see section 4.4).

Diacetylmorphine powder for inhalation is usually administered using a technique known as 'chasing the dragon'. The powder from the sachet is placed on a piece of aluminum foil and carefully heated from below with a cigarette lighter to melt and vaporize it. The arising fumes are inhaled through a suitable straw or tube. The heating is stopped in between inhalations and the substance is moved around on the aluminum foil. Overheating leading to charring and burning should be avoided. Sachets and straws must be handed back to supervising staff for destruction after supervised diacetylmorphine self-administration.

4.3 Contraindications

- Hypersensitivity to diacetylmorphine or any component of the drug product
- Severe respiratory depression or cyanosis
- Exacerbated chronic obstructive airway disease
- Diacetylmorphine powder for inhalation has not been studied in children and use in children is therefore contraindicated.

4.4 Special warnings and precautions for use

- Avoid exposure to the contents of the sachets since diacetylmorphine powder may cause contact dermatitis.
- Diacetylmorphine should not be administered to patients with head injuries or raised intracranial
- pressure.
- Care should be exercised in treating patients with mild to moderate respiratory depression or obstructive airways disease, since diacetylmorphine may aggravate these conditions.
- Caution should be exercised in case of concurrent administration of monoamine oxidase inhibitors or within two weeks of discontinuation of treatment with these products.
- Caution should be exercised in treating patients with epilepsy or allergic skin reactions, and in elderly or debilitated patients.
- Caution should be exercised in treating patients with hepatic or renal impairment: accumulation of morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) may occur in patients with moderate to severe renal impairment, and metabolism of diacetylmorphine could be altered significantly in patients with severe hepatic impairment.
- Based on reports from published studies, diacetylmorphine can cause hypotension in patients who already have conditions or drug therapy that interfere with the ability to maintain normal blood pressure.
- Careful consideration should be given before treating patients with myxoedema or hypothyroidism, adrenocortical insufficiency, toxic psychoses, central nervous system depression, prostatic hypertrophy or urethral stricture, kyphoscoliosis, acute alcoholism and delirium tremens, severe inflammatory bowel disease and severe diarrhea.

4.5 Interaction with other medicinal products and other forms of interaction

In the intended patient population, concurrent use or abuse of other sedative, hypnotic, or stimulant drugs (including alcohol) should be taken into consideration when determining the dosage of diacetylmorphine powder for inhalation vapour, as combination with these drugs can enhance the central depressant effects.

Caution should be exercised in treating patients on diacetylmorphine with oral or intravenous morphine, since both drugs share the same metabolic pathways and accumulation of metabolites could occur, especially in patients with hepatic or renal impairment.

Administration of drugs having anti-muscarinic activity (atropine and synthetic anticholinergics) may increase the risk of severe constipation and/or urinary retention.

It should be noted that there are no formal drug-drug interaction studies and that there is relatively little experience with long-term use of prescribed diacetylmorphine in combinations with other medications.

4.6 Pregnancy and lactation
There is little human data available regarding the use of diacetylmorphine during pregnancy.
In reports form the literature undesirable effects on animal offspring have been identified. Opiates cross the placenta. Administration of diacetylmorphine directly before parturition can result in respiratory depression in the neonate. When opiates are taken throughout pregnancy and up to parturition withdrawal effects may occur in the neonate.
Use of diacetylmorphine in pregnancy is therefore not recommended, unless strictly necessary.

There is limited information on diacetylmorphine levels in breast milk.
In view of the possible respiratory depressive effects of diacetylmorphine on the neonate it is not advisable for patients using diacetylmorphine to breast-feed.

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. Given the pharmacological effects of diacetylmorphine including sedation, driving or operating machinery should be avoided.

4.8 Undesirable effects
The most serious hazards of diacetylmorphine powder for inhalation vapour are respiratory depression and arrest, although circulatory depression, shock, and cardiac arrest can occur.

The most commonly observed adverse effects seen in studies in subjects with chronic treatment resistant diacetylmorphine dependency receiving diacetylmorphine powder for inhalation vapour for 12 months or more were infections; the incidence (approximately 36%) was similar to patients using methadone-alone. The occurrence of infections may be a result of the lifestyle of these patients, however it cannot be excluded that the immunosuppressive properties of opiates also play a role.

Adverse events which may be related to the use of diacetylmorphine powder for inhalation vapour given concomitantly with oral methadone and occurring with an incidence of >5% are: nausea and vomiting, influenza-like symptoms, respiratory symptoms (including cough, respiratory tract infections, dyspnea and asthma), occasional psychiatric disorders (including depression and psychotic manifestations), eczema and rash. The use of diacetylmorphine may increase the risk of epileptic seizures and psychoses in susceptible patients.

The very rare occurrence of leucoencephalopathy has been reported in the literature. Leucoencephalopathy has not been reported in the Dutch clinical studies. Very rarely, brief spells of bradycardia have been observed immediately after intravenous injection of diacetylmorphine.

4.9 Overdose
The symptoms of serious overdosage are respiratory depression, stupor or coma, muscle flaccidity, cold clammy skin, constricted pupils, and occasionally bradycardia and hypotension, and seizures.
In case of acute overdose, patent airways should be re-established and assisted ventilation instituted if indicated. Supportive measures should be instituted in the case of circulatory shock and pulmonary edema.

Overdosage should be treated by careful administration of the opiate antagonist naloxone.
In physically diacetylmorphine-dependent patients, administration of naloxone may result in a reversal of opioid effects and precipitate an abstinence syndrome. Refer to prescribing information of naloxone for details of proper usage.

5. PHARMACOLOGICAL PROPERTIES

ATC Code: N02AA09 **Group: opioids**

5.1 Pharmacodynamic properties

Diacetylmorphine is a narcotic analgesic, a synthetic derivative of morphine, which acts mainly on the opioid receptors in the central nervous system and smooth muscle. Opioids, including diacetylmorphine, stimulate μ opioid receptors and affect a wide range of physiological systems. They produce analgesia, affect mood, modulate reward mechanisms in the brain as shown in behavioural models and alter respiratory, cardiovascular, gastrointestinal, and neuroendocrine function. It is obvious that in this context, particularly the latter four aspects are relevant in adjusting the dosages of diacetylmorphine.

All opioids including diacetylmorphine induce tolerance and physical dependence with repeated use.

The safety and efficacy of medically co-prescribed inhaled diacetylmorphine was evaluated in a total of 394 patients who were participating in methadone treatment programmes. The principal evidence of the safety and efficacy comes from a 12-month, randomized study of adjunctive diacetylmorphine prescription, compared to methadone maintenance alone. After these 12 months there was a 6-month follow-up period during which those who had had methadone alone were permitted to receive add-on diacetylmorphine, in the co-prescribed diacetylmorphine group patients were given the most appropriate care but without diacetylmorphine.

The study population consisted of poorly functioning, chronically treatment-resistant patients with a diagnosis of diacetylmorphine dependency (DSM IV – 304.00) lasting five years or more and who predominantly administered diacetylmorphine by inhalation on a daily or near-daily basis. The participants had a long history of poly-drug use and unsatisfactory participation in addiction treatments, including long-term methadone maintenance. Patients experienced treatment needs with regard to their physical health, psychiatric status, and/or social functioning.

Treatment response was defined as a dichotomous, multi-domain outcome index containing the aspects physical health, mental status and social functioning. Twelve months of diacetylmorphine co-prescription with oral methadone resulted in a significantly larger responder rate as compared to treatment with oral methadone alone (p=0.0002). Patients responding to diacetylmorphine co-prescription generally showed improvement on more than one domain.

The mean daily dosage of co-prescribed diacetylmorphine for inhalation, the controlled study (n= 250) given for 6 or 12 months was respectively 520.4 mg/ day (SD 215.9 mg) and 484.4 mg (SD 200.9 mg), divided over 2-3 administrations per day. In open studies in which patients received inhaled diacetylmorphine for up to 12 months or more, the average daily dosages ranged between 586 mg (SD 213 mg) and 617 mg (SD 201.2 mg) /day divided over 2-3 administrations.

5.2 Pharmacokinetic properties

Absorption and distribution
After inhalation of diacetylmorphine powder for inhalation vapour via the technique known as ‘chasing the dragon’ (see 4.2) during a maximum of 30 minutes, the bioavailability of diacetylmorphine was found

to be about 45 – 50 % (based on excretion of total morphine and direct comparison with intravenous administration). After entering into the bloodstream, diacetylmorphine distributes rapidly over the body and into the central nervous system.

Metabolism
It is rapidly hydrolyzed to 6-acetylmorphine and subsequently to morphine by esterases in plasma and tissue. Diacetylmorphine, 6-acetylmorphine and morphine all possess opioid agonistic activity. The observed C_{max} of diacetylmorphine is very variable, which is at least in part due to the rapidly changing plasma concentrations of diacetylmorphine that make exact determination of C_{max} difficult.
Diacetylmorphine clearance is typically 500-2000 L/h, exceeding by far the combined renal and hepatic blood flow, due to the extra-hepatic hydrolysis. Plasma half-life values for diacetylmorphine, 6-acetylmorphine and morphine are in the range of 3-5 min, 20 min, and 180 min, respectively, which is reflected in the much higher AUC of morphine compared to that of diacetylmorphine.
Morphine in turn is glucuronated to morphine-3-glucuronide and morphine-6-glucuronide in a ratio of about seven to one.

Elimination
The main route of elimination of diacetylmorphine is via the kidneys as 6-acetylmorphine (1.5%), morphine (10%) or morphine glucuronides (55%). Part of the morphine glucuronides is excreted into the bile and re-enters the circulation as morphine via enterohepatic recirculation.

Kinetic parameters after diacetylmorphine base/caffeine inhalation in opioid addicted subjects**

Dose Level	Statistic	Dose (mg)	t_{max} (min)	C_{max}/D (ng.mL/mg)	$AUC_{0-\infty}/D$ (h*µg/L/mg	Cl/F (L/h)
Maintenance	Mean	283.3	10.1	2.57	0.632	1989
	CV%			56	53	53

** derived from study CCBH.KNL 40058 - reanalysis

Drug-drug interactions
Drugs interacting with the hydrolysis of diacetylmorphine and 6-acetylmorphine are expected to increase exposure. Ethanol enhances the risk of diacetylmorphine overdose, possibly by inhibition of the hydrolysis.
Drugs inhibiting the glucuronidation of morphine may increase morphine levels, but may also prevent the formation of the opioid morphine-6-glucuronide. Although many classes of drugs have shown to inhibit glucuronidation in vitro, the clinical relevance is not clear.
Similarly, drugs inhibiting the extrusion pumps P-glycoprotein and Organic Anion Transporter Proteins (OATPs) may theoretically increase exposure.

5.3 Preclinical safety data
No specific preclinical toxicological studies have been performed which are designed to support a thorough, quantitative risk assessment of diacetylmorphine powder for inhalation vapour.
However, the information available from studies conducted mainly in rodents indicates that the main organ involved in the toxicity of diacetylmorphine is the central nervous system. At low doses, classic opiate-like effects appear, at higher doses sedation, respiratory depression, and convulsions are induced, leading to death at high doses.
The target organs of toxicity after repeated administration of diacetylmorphine appear to be: the testes, the skeletal muscle and the immune system.
Reproductive toxicity studies mainly show the potential of diacetylmorphine to adversely affect the development of the nervous system leading to structural, functional and behavioural deficits.

Diacetylmorphine has the potential to promote the occurrence of chromosomal damage but does not appear to be a direct genotoxic agent. Carcinogenicity studies have not been performed with diacetylmorphine, but its indirect effects on the chromosomes together with reduced immune competence of the patients may lead to an increased risk of developing tumors.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipient(s)
Water-free caffeine.

6.2 Incompatibilities
None known.
Diacetylmorphine should not be mixed with other drugs/substances.

6.3 Shelf-life
2 years

6.4 Special precautions for storage
Do not store at temperatures in excess of 25°C.

6.5 Nature and contents of container
Each package contains 50 sachets (50 x 65 mm), consisting of aluminum foil with a low-density polyethylene coating on the inside and a paper coating on the outside.

6.6 Instructions for use and handling
Medical staff: Avoid skin contact with the contents of the sachet, occupational exposure to diacetylmorphine has been associated with contact dermatitis. Avoid inhaling the diacetylmorphine fumes.

7. MARKETING AUTHORISATION HOLDER
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8. MARKETING AUTHORISATION NUMBER(S)

Diacetylmorfine 75 mg, powder for inhalation vapour – RVG 33464
Diacetylmorfine 100 mg, powder for inhalation vapour – RVG 33465
Diacetylmorfine 150 mg, powder for inhalation vapour – RVG 33466
Diacetylmorfine 200 mg, powder for inhalation vapour – RVG 33467

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

14 December 2006.