

IPAR
Public Assessment Report

Scientific discussion

IE/H/170/03-04

**Midazolam Injection BP 2mg/ml & 5mg/ml
Solution for injection or infusion**

This module reflects the scientific discussion for the approval of Midazolam. The procedure was finalised at 19/12/2007. For information on changes after this date please refer to the module 'Update'.

I INTRODUCTION

Following the synthesis of chlordiazepoxide in 1957 and its introduction into clinical medicine in 1961, more than 3,000 benzodiazepines have been synthesized in the search for other therapeutically useful compounds in this class. Midazolam was first synthesized over 30 years ago and it was selected for clinical trials because of its short duration of action and the water-solubility and stability of its salts.

Based on the review of data on quality safety and efficacy, the IMB granted marketing authorisations for Midazolam Injection BP 2mg/ml & 5mg/ml. National marketing authorisations were granted in Ireland for the indications detailed below on the 1st of September 2006.

This Mutual Recognition (MR) application concerns a generic version of midazolam and is submitted under the provisions for abridged applications under Art.10.1 (a) (iii) of Directive 2001/83/EC as amended, and is a “generic” application.

With Ireland as the Reference Member State in this Mutual Recognition Procedure, Taro Pharmaceuticals Ireland Limited, is applying for the Marketing Authorisation for Midazolam Injection BP 2mg/ml and 5mg/ml in the United Kingdom. Midazolam Injection BP 5mg/ml and Midazolam Injection BP 2mg/ml (Taro Pharmaceuticals Ireland Ltd) are simple aqueous solutions containing midazolam 5mg per ml and 2mg per ml, respectively. The originator products are Hypnovel (10mg/2ml and 10mg/5ml Ampoules) by Roche Products Limited.

The products are simple aqueous solutions of midazolam 5 mg per ml and 2 mg per ml, the active substance, in hydrochloric acid for solubility, sodium chloride for adjustment of tonicity, and sodium hydroxide for pH adjustment. In terms of the active substance, pharmaceutical form and dose proportionality, the two strengths of midazolam injection manufactured by Taro Pharmaceuticals Ireland Ltd. are essentially similar to the corresponding strengths of Hypnovel Ampoules, which have been authorised by the European Community for more than 10 years and which are marketed in the Member State in which this application is made.

The Applicant has supplied a comprehensive and extensive list of literature references that is relevant to the substantiation of this MAA. Comparative bioequivalence studies were not performed in line with the relevant guidance (*Note for Guidance on the Investigation of Bioavailability and Bioequivalence* CPMP/EWP/QWP/1401/98), which states that for parenteral solutions, the Applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised product.

The therapeutic indications, posology and method of administration proposed for Midazolam Injection BP 5 mg/ml and Midazolam Injection BP 2 mg/ml (Taro) are the same as those authorised for Hypnovel Ampoules 10 mg/2ml and Hypnovel Ampoules 10 mg/5 ml, respectively, in the Member State in which this application is made as follows:

In adults and children

- Conscious sedation before and during diagnostic or therapeutic procedures with or without local anaesthesia,
- Premedication before induction of anaesthesia,
- Sedation in Intensive Care Units.

In adults

- Induction of anaesthesia,
- As an induction agent or as a sedative component in combined anaesthesia.

Midazolam belongs to the pharmacological class of benzodiazepines. Benzodiazepines, as adjuncts to anaesthesia, are

used as anxiolytic agents, to induce amnesia and sedation prior to the induction of anaesthesia or for sedation during procedures not requiring general anaesthesia. The site of action of Midazolam has not yet been fully elucidated, but it appears to be mediated through the inhibitory neurotransmitter gamma-aminobutyric acid. It appears to act at the limbic, thalamic and hypothalamic levels of the CNS, producing anxiolytic, sedative, hypnotic, skeletal muscle relaxant and anticonvulsant effects. Benzodiazepines are capable of producing all levels of CNS depression-from mild sedation to hypnosis to coma. Midazolam has a sedative potency of 1.5-2.5 times that of diazepam, but it may be as high as 3-4 times as potent. Midazolam acts rapidly after IM or IV administration, but its half-life is 2 hours, making it an ideal adjunct for anaesthesia. When administered preoperatively, Midazolam relieves anxiety and provides sedation, light anaesthesia and anterograde amnesia of perioperative events.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its National authorisation.

The manufacturing authorisation of the manufacturing site, located in the Republic of Ireland, has been granted by the Inspectorate of the Irish Medicines Board on 17th May 2006.

An updated Module 3 has been provided by the applicant incorporating the responses to queries raised during the national authorisation.

II QUALITY ASPECTS

II.1 Introduction

This application for Midazolam Injection BP is submitted in accordance with Directive 2001/83/EC Article 10.1. generic application. The product is a solution for injection or infusion with known drug substance midazolam. Two strengths of the product are applied for 2 mg/ml and 5 mg/ml. The national authorisations in Ireland were granted on 1st September 2006.

II.2 2.2 Drug Substance

The active substance is Midazolam, a known drug substance described in the European Pharmacopoeia (Ph. Eur.), which is manufactured in accordance with Good Manufacturing Practice (GMP). The Active Substance Master File (ASMF) procedure is used for the active substance.

The active substance specification is considered adequate to control the quality of the active substance and meets the requirements of the monograph in the Ph. Eur. Batch analytical data demonstrating compliance with the specification have been provided for 3 representative batches.

Appropriate stability data have been generated supporting a retest period of 2 years and a shelf life of 5 years.

II.3 Medicinal Product

II.3.1 Composition

The product is a preservative free, clear, colourless or slightly yellow sterile aqueous solution. Two strengths are applied for 2mg/ml and 5mg/ml. Both strengths are to be supplied in translucent polypropylene (PP) ampoules.

The active substance is Midazolam. Each ml contains either 2mg or 5mg Midazolam. The excipients are: Sodium Chloride, Hydrochloric acid, Sodium Hydroxide (10% w/w), Water for Injections and Nitrogen (not present in the final product).

II.3.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the

relevant European guidelines. The purpose of the development was to develop a product bioequivalent to the reference product Hypnovel Injection. A comparative analysis between one batch of each strength of the reference product and 1 batch of each strength of Taro Midazolam Injection has been conducted and indicates that both products are equivalent.

II.3.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP). The product is manufactured using conventional manufacturing techniques. A commitment has been given that the first 3 production batches for each strength and batch size shall be validated post-authorisation.

II.3.4 Control of Excipients

All excipients comply with their respective European Pharmacopoeia monographs. There are no excipients of human or animal origin used in the manufacture of the product. There are no novel excipients used in the manufacture of the product

II.3.5 Control of Finished Product

The finished product specification is adequate to control the relevant parameters for the dosage form. The release specifications for the drug product are based on the British Pharmacopoeia (BP) monograph for Midazolam Injection and the standard requirements associated with parenteral preparations. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for analytical methods have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

II.3.6 Packaging Material

The product is presented as translucent polypropylene ampoules which are manufactured as part of the product filling process. Evidence has been provided that the polypropylene ampoules comply with Ph. Eur. requirements.

II.3.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product for 18 months when stored below 25°C in the outer carton in order to protect from light.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Midazolam Injection BP 2mg/ml & 5mg/ml.

III NON-CLINICAL ASPECTS

Abridged applications avoid the need for repetitive tests on animals. The toxicology of midazolam in animals has been extensively investigated. The toxicity profile of midazolam is essentially that of the benzodiazepines in general and the data reviewed support the continued use of the drug under the conditions of use proposed. There is no relevant product non-clinical information that merits inclusion in this section of the review.

IV CLINICAL ASPECTS

IV.1 Introduction

Midazolam is an imidazobenzodiazepine, differing structurally from other benzodiazepines by the presence of an imidazole ring fused at positions 1 and 2 of the benzodiazepines nucleus. Midazolam injection is composed of 8-

Chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo [1, 5-a] benzodiazepine hydrochloride, with hydrochloric acid and sodium hydroxide added to adjust pH. Midazolam has all the characteristic effects of the benzodiazepines: sleep-inducing, sedative, anxiolytic, anti-convulsant, muscle relaxing and amnesic. Although benzodiazepine receptors have been identified in various body tissues, including the heart and skeletal muscle, their predominance appears to be in the central nervous system. Benzodiazepines enhance the inhibitory action of the amino acid neurotransmitter gamma-aminobutyric acid (GABA). *In vitro* studies of receptor binding capacity have shown that midazolam has approximately twice the affinity of diazepam for the benzodiazepine receptor.

IV.2 Pharmacokinetics

Absorption

Following intramuscular injection, absorption of midazolam is rapid, with peak plasma concentrations within 30 minutes and an absolute bioavailability of more than 90%. After rectal administration, midazolam is absorbed rapidly and peak plasma concentrations are reached within about 30 minutes.

Distribution

The volumes of distribution of the benzodiazepines in general are large. Midazolam has a volume of distribution of 0.8 - 1.2 L/kg; the volume of distribution of midazolam is greater in elderly than in younger subjects, in women than in men and in obese than in non-obese subjects. After intravenous administration of midazolam to healthy subjects, the drug undergoes a phase of rapid distribution into deeper compartments, followed by a slower phase of disappearance due mainly to biotransformation. The distribution half-life of midazolam is 25-30 minutes and the elimination half-life is 1.5-3 hours. Midazolam is extensively bound to plasma proteins, only about 4% being unbound. The unbound fraction is higher in patients with chronic renal failure than in those with normal renal function. Atypically of the benzodiazepines, almost no midazolam is detected in the cerebrospinal fluid following a single dose. Midazolam crosses the placenta and enters the foetal circulation, and the drug has been detected in breast milk at mean milk to plasma ratio of 0.15.

Metabolism

Midazolam undergoes biotransformation by hepatic microsomal oxidation followed by conjunction with glucuronic acid. Initially, midazolam is hydroxylated by cytochrome P450-3A4 to its major metabolite, alpha-hydroxy-midazolam, and minimally to the inactive metabolites 4-hydroxy-midazolam and alpha, 4-dihydroxymidazolam. All of these metabolites are excreted in the urine as glucuronide conjugates. Alpha-hydroxy-midazolam is an active metabolite and may contribute to the pharmacological effect of midazolam.

Elimination

Midazolam is eliminated almost exclusively by metabolic processes. The drug has a short elimination half-life of 1.5-3 hours. Prolongation of the elimination half-life has been reported in neonates, the elderly, patients with hepatic impairment, obese individuals, patients with congestive cardiac failure and in critically ill patients. A shorter elimination half-life (mean 1.17 hours) has been reported in children aged 3-10 years compared to adults. The principal metabolite of midazolam, alpha hydroxymidazolam, has a short elimination half-life of about one hour.

Plasma clearance of midazolam has been calculated at 5.8-9.0 ml/min/kg in healthy subjects and is greater in the supine position compared to values in the same subjects while ambulant, probably reflecting the increase in hepatic blood flow that occurs in the supine position. The principal route of excretion is through the kidneys. Midazolam is excreted in urine mainly as metabolites, with less than 0.5% recoverable in urine as unchanged drug.

Interactions

There are several clinically relevant pharmacokinetic interactions between midazolam and other medicinal products. Midazolam is metabolised in the liver by the isoenzyme CYP3A4 of the cytochrome P450 system. Agents that inhibit or induce CYP3A4 may interact with midazolam.

- Macrolide Antibiotics: Erythromycin and clarithromycin inhibit the metabolism of midazolam, resulting in increased plasma midazolam concentrations and increased sedation.
- Azole Antifungals: Itraconazole, fluconazole and ketoconazole increased the plasma levels of midazolam, increasing and prolonging its sedative effect. As in the case of midazolam - macrolide antibiotic interaction, the

CYP3A4 isoenzyme appears to be involved.

- Saquinavir: The protease inhibitor saquinavir increased the plasma concentration of midazolam and poses the risk of prolonged sedation.
- Cimetidine and Ranitidine: Oral administration of Cimetidine 800 mg increased the mean steady-state plasma concentration of intravenous midazolam, whereas oral ranitidine 300 mg had no effect. In a subsequent study, co-administration of cimetidine 300 mg six hourly or ranitidine 150 mg every 12 hours produced no significant differences in the pharmacokinetics of midazolam administered either intravenously or orally.
- Calcium Channel Blockers: The effects of oral diltiazem or verapamil on the pharmacokinetics of oral midazolam have been investigated. Both calcium channel blockers caused a significant increase in the AUC and half-life of midazolam, resulting in increased sedation, decreased psychomotor performance and amnesia.

IV.3 Pharmacodynamics

Midazolam is a benzodiazepine derivative. The term benzodiazepine refers to the portion of the structure composed of a benzene ring fused to a seven-membered diazepine ring. Midazolam is an imidazobenzodiazepine. These compounds have an imidazole ring fused on position 1, 2 of the diazepine ring. The fused imidazole ring modifies the properties of midazolam in respect of basicity, stability in aqueous solutions and proneness to metabolic alteration. The basicity of the imidazole ring allows the preparation of salts, e.g. with hydrochloric, maleic or lactic acid, which are easily soluble in water. In addition, the fused imidazole ring is very stable to hydrolysis. Furthermore, the methyl group in position 1, on the fused imidazole ring is responsible for the short duration of action of midazolam.

Midazolam has all the characteristic effects of the benzodiazepines. Although benzodiazepine receptors have been identified in various body tissues, including the heart and skeletal muscle, their predominance appears to be in the central nervous system. Benzodiazepines enhance the inhibitory action of the amino acid neurotransmitter gamma-aminobutyric acid (GABA). *In vitro* studies of receptor binding capacity have shown that midazolam has approximately twice the affinity of diazepam for the benzodiazepine receptor. The pharmacodynamic effects of midazolam have been verified in numerous test settings using different observer rating scales, self-ratings, visual analogue scales and psychomotor tests in healthy subjects and in hospitalised patients. At intravenous doses below 5 mg, the anxiolytic, anticonvulsant and sedative properties of midazolam are present. For a deep hypnotic effect under stressful conditions, intravenous doses in excess of 10 mg may be necessary.

Early studies established the anterograde amnesic action of intravenous midazolam, which was maximal at 2 to 5 minutes after injection. There is a similar time course of action of midazolam and diazepam, with the former having a slightly shorter duration of effect. Intravenous midazolam acts on higher respiratory centers and can lead to respiratory depression and apnoea. The muscle relaxant property of midazolam may reduce the activity of the airway muscular system, thereby increasing inspiratory resistance.

As with the injectable benzodiazepines in general, midazolam is reported to cause minimal haemodynamic changes in animals and in man. Known cardiovascular effects of midazolam consist of a decrease in blood pressure of about 15%, which involves a decrease in systemic vascular resistance, venodilatation and a decrease in myocardial contractility.

The minimum effective plasma concentration of midazolam has been reported to range between 20 and 80 ng/ml. At concentrations above 80 ng/ml, sedation, muscle relaxation, ataxia and amnesia were observed; sleep occurred at concentrations above 100 ng/ml.

IV.4 Clinical efficacy

Claim for essential similarity

The application to which this Clinical Overview relates is an abridged application in accordance with article 10.1(a) (iii) of Directive 2001/83/EC (so called 'generic application'). Midazolam 5 mg/ml Injection BP and Midazolam 2 mg/ml Injection BP manufactured by Taro Pharmaceuticals Ireland Ltd are generic forms of the well-established Hypnovel Ampoules 10 mg/2 ml and Hypnovel Ampoules 10 mg/5 ml, respectively. The products are simple aqueous solutions of midazolam 5 mg per ml and 2 mg per ml, the active substance, in hydrochloric acid for solubility, sodium

chloride for adjustment of tonicity, and sodium hydroxide for pH adjustment. In terms of the active substance, pharmaceutical form and dose proportionality, the two strengths of midazolam injection manufactured by Taro Pharmaceuticals Ireland Ltd. are essentially similar to the corresponding strengths of Hypnovel Ampoules which have been authorised by the European Community for more than 10 years and which are marketed in the Member State in which this application is made. The therapeutic indications, posology and method of administration proposed for Midazolam 5 mg/ml Injection BP and Midazolam 2 mg/ml Injection BP (Taro) are the same as those authorised for Hypnovel Ampoules 10 mg/2ml and Hypnovel Ampoules 10 mg/5 ml, respectively, in the Member State in which this application is made.

Bioequivalence

Comparative bioequivalence studies were not performed in line with the relevant guidance (*Note for Guidance on the Investigation of Bioavailability and Bioequivalence* CPMP/EWP/QWP/1401/98), which states that for parenteral solutions, the Applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised product.

Efficacy of the product in the intended population

Although midazolam has anti-convulsant and muscle relaxant properties, its clinical use is primarily reserved for premedication, conscious sedation and induction of anaesthesia, and for sedation in the ICU setting. Midazolam is characterised by a short onset of action and a short duration of effect in healthy subjects. An association between midazolam plasma concentrations and the degree of sedation has been established in both children and adults, but this association is of limited clinical utility as plasma levels are not readily available in practice. However, midazolam has been shown to exert its different pharmacological effects with increasing doses and this feature can be utilized to achieve the desired effect through dose titration; at low doses of approximately 2 -5 mg, anxiolytic and tranquillizing effects are predominant, whereas more obvious sedative, muscle-relaxant and anticonvulsant effects are achieved at doses of 5 - 10 mg, and higher doses may be sufficient for induction of anaesthesia.

Main studies performed on human plasma, in healthy volunteers and clinical experience

Following the synthesis of chlordiazepoxide in 1957 and its introduction into clinical medicine in 1961, more than 3,000 benzodiazepines have been synthesized in the search for other therapeutically useful compounds in this class. Midazolam was first synthesized over 30 years ago and it was selected for clinical trials because of its short duration of action and the water-solubility and stability of its salts. Large numbers of clinical studies have been conducted which demonstrate the efficacy of midazolam as a pre-medication, sedative and induction agent for general anaesthesia, and these have been reviewed by a number of authors. In addition, the efficacy of midazolam for the proposed indications has been well established through extensive, worldwide clinical experience.

The Applicant has supplied a comprehensive and extensive list of literature references that is relevant to the substantiation of this marketing authorization application by means of an abridged application under Art.10.1 (a) (iii) of Directive 2001/83/EC.

Overall Conclusions on Clinical Efficacy

Midazolam's clinical efficacy is well established as a pre-medication, sedative and as an induction agent for general anaesthesia. As already stated in this report, midazolam's efficacy for the proposed indications have been well established through extensive global clinical experience.

IV.5 Clinical safety

Midazolam hydrochloride is a short acting benzodiazepine whose clinical applications include preoperative sedation and conscious sedation prior to diagnostic or radiographic procedures via the direct intravenous or continuous intravenous routes. The safety (and efficacy) of Midazolam Hydrochloride Injection is well established. It is safe (and effective) in both the paediatric and adult population.

Adverse effects characteristic of the pharmacological class

Although midazolam is relatively free of adverse effects when used alone, it displays a number of adverse effects that are characteristic of benzodiazepines as a class. Central nervous system reactions may occur with midazolam, including

drowsiness, confusion and headache, and these are dose dependent. Disinhibition reactions such as paradoxical hostility, aggression and rage have been reported, rarely. Prolonged infusions of midazolam for several days to weeks have been associated with benzodiazepine-withdrawal symptoms, including seizures. Midazolam, like other benzodiazepines, produces anterograde amnesia, the incidence and duration of which appear to be dose-related; prolonged amnesia has been reported. Gastro-intestinal reactions that are typical of the benzodiazepines, such as nausea, vomiting, constipation and dry mouth, have been reported with midazolam.

Relation of adverse events to dose, dose regimen and treatment duration

Midazolam exerts its different pharmacological effects with increasing doses. The dosage, dose regimen and treatment duration for midazolam injection, which are designed to optimise safety whilst achieving the desired level of sedation, have been well defined through clinical studies and through wide clinical experience.

Long-term safety

Prolonged use of benzodiazepines is associated with dependence. Intravenous infusions of midazolam for several days to weeks have been associated with acute benzodiazepine withdrawal symptoms, including seizures. Treatment with midazolam may be prolonged in the ICU setting and, as the risk of withdrawal symptoms is greater after abrupt discontinuation of benzodiazepines, discontinuation of midazolam should be gradual. Tolerance to sedation has been reported in association with prolonged use of benzodiazepines.

Adverse events

Fluctuations in the respiratory rate, pulse rate and blood pressure are the most commonly reported adverse events. Hiccoughs, nausea, vomiting and headache may occur, and pain at the injection site has been reported, although less frequently than with diazepam.

IV administration of midazolam may depress myocardial contractility and cause apnoea. Severe cardiorespiratory adverse events have rarely occurred and include respiratory depression, apnoea and respiratory and or cardiac death. Midazolam should only be used when appropriate resuscitation facilities are available. Severe cardiorespiratory depression may occur: there have been reports of apnoea, respiratory arrest and cardiac arrest, particularly in the elderly. There have also been a number of case reports of ventricular bigeminy and trigeminy and of ventricular tachycardia. Angioedema, bronchoconstriction and anaphylactoid reactions have also been reported in association with the use of midazolam.

Safety in special populations

Paediatric patients of less than 6 months of age are particularly vulnerable to airway obstruction and hypoventilation; therefore it is essential to monitor the respiratory rate and oxygen saturation in these patients whilst titrating the dose of midazolam with small increments to clinical effect.

When midazolam is used for pre-medication, patients should be observed carefully, as the inter-individual sensitivity varies and symptoms of overdose may occur. Midazolam is a potent sedative that required dose titration and slow administration. The level of sedation should be assessed, regularly, in all patients to avoid over sedation with midazolam. Patients considered to be at high risk should be continuously monitored for early signs of alteration in vital functions, including haemodynamic instability and respiratory depression.

As detailed in the proposed Summary of Product Characteristics, the following population sub-groups are deemed to be high-risk patients with regard to their susceptibility to adverse events associated with midazolam:

- Adults over age 60 years
- Chronically ill or debilitated patients, e.g.
- Patients with chronic respiratory insufficiency
- Patients with chronic renal failure, impaired hepatic function or impaired cardiac function.
- Paediatric patients, especially those with cardiovascular instability.

Overdose; potential for dependence; rebound phenomena; abuse.

The symptoms of overdose are mainly an intensification of the pharmacological effects of midazolam; drowsiness; confusion; lethargy and muscle relaxation or paradoxical excitation. More serious features of overdose would be areflexia, hypotension, cardiorespiratory depression and coma. Flumazenil, a benzodiazepine antagonist, is indicated in cases of severe intoxication accompanied by coma or respiratory depression, although caution is required when using

flumazenil in case of mixed drug overdose and in patients with epilepsy already treated with benzodiazepines. Flumazenil should not be used in patients treated with tricyclic antidepressants, epileptogenic drugs or patients with ECG abnormalities (QRS or QT prolongation). Use of midazolam, even in therapeutic doses, may lead to the development of physical dependence after prolonged I.V. administration; abrupt discontinuation may be accompanied by withdrawal symptoms, including convulsions. The risk of dependence increases with dose and duration of treatment. There is no evidence of the problem of rebound phenomena arising in association with midazolam. As with other benzodiazepines, midazolam has the potential for abuse.

IV.6 Discussion on the clinical aspects

Significant safety findings relate mainly to the central depressant effects of midazolam that are typical of the benzodiazepines as a class. The measures to enhance safety, which include individual dose titration, slow administration and careful monitoring of the patient, are set out in the proposed prescribing information. The optimal dose ranges and dose regimens for midazolam have been well established. As there is large inter-individual variation in the response to midazolam, the dose must be carefully titrated against the response of the patient in order to optimise safety whilst achieving the desired level of sedation. As previously discussed, certain sub-populations have been defined as high-risk patients with regard to their susceptibility to midazolam-related adverse effects. Due consideration is given to these patient groups in the proposed prescribing information. Known and potential interactions are well documented and are included in the proposed prescribing information.

The sedative, amnesic and muscular impairment effects of midazolam may adversely affect ability to drive or to operate machinery, and these effects are taken into account in the proposed prescribing information.

V OVERALL CONCLUSIONS

Midazolam injection is a potent, short-acting sedative and sleep-inducing drug. Abridged applications avoid the need for repetitive tests on humans. There is a vast amount of accumulated experience with the use of midazolam injection since it was first introduced into clinical practice approximately 20 years ago. The efficacy of midazolam injection has been, therefore, firmly established. The safety profile of midazolam is likewise well-defined and no new or different safety issues have been identified in the course of this review. Furthermore, no recent regulatory actions related to safety have been found during the preparation of this review.

Overall the dossier is of good quality and the applicant has provided relevant literature references and copies of the references to support this application under Art.10.1 (a) (iii) of Directive 2001/83/EC. No significant clinical issues were raised during the assessment of the application by either the RMS or the CMS involved. A number of quality questions were raised by the CMS and were resolved during the procedure.

The clinical content of the Summary of Product Characteristics for this product is identical to the Summary of Product Characteristics for the reference product. There are a number of differences in the pharmaceutical content. No amendments are required to the SPC text. Readability testing was performed on the Patient Information Leaflet. The Patient Information Leaflet was readable and understandable by all the participants in the test.

The overall risk/benefit balance for Midazolam Injection BP 2mg/ml and Midazolam Injection BP 5mg/ml is considered positive and the application was recommended for approval accordingly. Day 90 of the MR procedure was 19th December 2007 and the procedure was considered as successfully concluded on that date. The future common renewal date will be 1st September 2011 based on the first approval in Ireland.