**DEPODUR 10MG/1ML SUSPENSION FOR INJECTION (MORPHINE SULPHATE PENTAHYDRATE)**

PL20334/0002

**DEPODUR 15MG/1.5ML SUSPENSION FOR INJECTION (MORPHINE SULPHATE PENTAHYDRATE)**

PL20334/0003

**DEPODUR 20MG/2ML SUSPENSION FOR INJECTION (MORPHINE SULPHATE PENTAHYDRATE)**

PL20334/0004

**UKPAR**

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DEPODUR SUSPENSION FOR INJECTION

PL20334/0002-4

LAY SUMMARY

The MHRA granted SkyePharma PLC Marketing Authorisations (licences) for the medicinal product Depodur 10mg/1ml Suspension for Injection (PL 20334/0002), Depodur 15mg/1.5ml Suspension for Injection (PL 20334/0003) and Depodur 20mg/2ml Suspension for Injection (PL 20334/0004) on the 20th April 2006. This is a prescription only medicine (POM), for the relief of post-operative pain following major orthopaedic, abdominal or pelvic surgery.

Depodur Suspension for Injection is for epidural administration only. It contains the active ingredient Morphine sulphate pentahydrate which is a natural opioid alkaloid and is used to provide relief from pain. Depodur Suspension for Injection is an aqueous suspension of lipid-based particles, from which the active drug (morphine) is released gradually over a number of hours in order to achieve a long duration of pain relief.

The applicant has supplied scientific literature to demonstrate that the active substance in Depodur Suspension for Injection has been in well-established medicinal with acceptable levels of effectiveness and safety. The clinical data presented to the MHRA, pre licensing, demonstrated the safety and effectiveness of Depodur Suspension for Injection given as a single epidural injection to provide a sustained-release pain-killer. There were no significant safety concerns, provided that patients are closely monitored for 48 hours following administration of the product. It was therefore judged that the benefits of using Depodur Suspension for Injection outweigh the risks. Hence Marketing Authorisations have been granted.
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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Depodur Suspension for Injection (PL 20334/0002-4) to SkyePharma PLC on 20th April 2006. The products are Prescription Only Medicines (POM), available on special prescription.

The application was submitted as a ‘bibliographic application’, under article 10(a) [formerly 10.1 (a) (ii)] of Directive 2001/83/EC. The scientific literature demonstrated that the active substance in Depodur Suspension for Injection has been in well-established medicinal use with acceptable efficacy and safety. Clinical data supplied showed that the safety and effectiveness of the new product Depodur Suspension for Injection given as a single epidural injection was satisfactory, provided that patients receive high dependency monitoring for 48 hours following administration of the product.

Depodur Suspension for Injection is a sustained-release formulation containing the active ingredient morphine sulphate pentahydrate, a natural opium alkaloid, and is indicated for the relief of post-operative pain for up to 48 hours, when given as a single epidural injection.

These applications for Depodur Suspension for Injection (10mg/1ml, 15mg/1.5ml and 20mg/2ml) were submitted at the same time and were assessed concurrently. Consequently, all sections of this Scientific Discussion refer to all products.
1. INTRODUCTION

These national abridged applications are for suspensions for injection containing 10mg/ml morphine sulfate pentahydrate in 1ml, 1.5ml and 2ml glass vials, for epidural use only. The applicant has proposed that the products are indicated for the relief of post-operative pain for up to 48 hours.

All references in this report to morphine sulfate or morphine sulphate refer to the pentahydrate, unless otherwise specified.

These applications have been made under Article 10(a) [formerly article 10.1(a)(ii)] of Directive 2001/83/EC (so called ‘bibliographic application’). This legal basis is acceptable.

These products will only be available on a special prescription (CD) in accordance with Article 71 of Directive 2001/83/EC.

Formal Scientific Advice was provided by CPMP and by the UK, France, The Netherlands and Ireland on pharmaceutical, pre-clinical and clinical strategy prior to submitting these applications. Copies of relevant documentation from meetings/requests have been included in the dossiers.

The proposed products have not been authorised to the applicant or to a related company in any other European Union (EU) member state. The products have been authorised in the USA since May 2004.

2. COMMON TECHNICAL DOCUMENT SUMMARIES

2.1 INTRODUCTION

A brief but satisfactory introduction has been provided.

2.2 QUALITY OVERALL SUMMARY (QOS)

A satisfactory Quality Overall Summary has been provided.

3. ACTIVE SUBSTANCE

3.1 GENERAL INFORMATION

3.1.1 Nomenclature
INN: morphine sulfate
morphine sulfate pentahydrate
Morphine Sulphate Ph Eur
Morphine Sulfate USP

Chemical names:
(i) 7,8-Didehydro-4,5α-epoxy-17-methylmorphinan-3,6α-diol sulfate (2:1) (salt), pentahydrate
(ii) Morphinan-3,6-diol, 7,8-didehydro-4,5-epoxy-17-methyl, (5α, 6α)-, sulfate (2:1) (salt), pentahydrate

CAS Number: 6211-15-0

3.1.2 Structure

\((C_{17}H_{19}NO_3)_2\cdot H_2SO_4 \cdot 5H_2O\)  \(\text{MW: 758.85}\)

3.1.3 General Properties

Fine, odourless, white powder that may yellow slightly with age. Soluble in water (1g in 15.5ml), very slightly soluble in ethanol (1g in 565ml) at 25°C, practically insoluble in toluene. The pH of an aqueous 15mg/ml solution is approximately 4.8.

Water of hydration is lost between 100-130°C. The anhydrous form melts with decomposition at approximately 250°C.

The pKₐ for morphine are 7.87 and 9.85.

3.2 MANUFACTURE

3.2.1 Manufacturer

A copy of a letter of access dated 09 October 2003 and the Applicant’s Part of the EDMF have been provided for the specified source of active substance. This version is identical to that supplied direct to the MHRA by the DMF holder.

3.2.2 Manufacturing process description and process controls

Details of the manufacturing process have been provided.

No organic solvents (including those described in the USP as organic volatile impurities) are used in the process.

3.2.3 Control of materials

Confirmation has been provided that morphine sulfate is a natural product of vegetable origin. No TSE risk is associated with this active substance.

3.3 CHARACTERISATION
3.3.1 Elucidation of structure and other characteristics

Morphine possesses 5 chiral centres, although as the bridge system must be cis, only 8 pairs of enantiomers are possible. Only 1 enantiomer is derived from natural sources. Specific rotation is -107° to -109.5° at 25°C (20mg/ml solution in water, on anhydrous basis)

The structure of morphine sulfate pentahydrate has been confirmed by IR, C-NMR and H-NMR. Copies of spectra have been provided.

3.3.2 Impurities

The transparency statement in the Ph Eur monograph has entries for codeine (impurity A), 2,2’-bimorphine (pseudomorphine - impurity B) and morphine N-oxide (impurity C).

Pseudomorphine and individual unknown impurities are controlled to levels at or below the ICH threshold for qualification (0.15%). These impurities therefore need no further qualification. The other potential related substances are morphine metabolites (according to section 2.6.6 Toxicology Written Summary). Codeine is a known therapeutic agent in its own right. The specified potential impurities are therefore considered qualified at the levels proposed by the applicant.

3.4 CONTROL OF ACTIVE SUBSTANCE

3.4.1 Specification

Batches of active substance are tested by the Active Ingredient Manufacturer (AIM), the finished product manufacturer or by a contract analytical laboratory.

Ethanol is controlled in the Ph Eur monograph and in the specification proposed by the active substance manufacturer, although it is not used in the manufacturing process. The AIM certifies morphine sulfate pentahydrate as organic volatile impurity-free and ethanol-free.

The active substance specification is satisfactory.

3.4.2 Analytical procedures / validation

The specification provided includes the requirements of the Ph Eur monograph for morphine sulphate (sic) with testing using the Ph Eur methods or equivalent USP methods. The applicant has provided a satisfactory comparison of Ph Eur and USP methods to support use of the methods described. The applicant has confirmed that where a USP method is used, the active substance would comply with the Ph Eur if tested by the method described in the Ph Eur.

Details of the analytical methods used by the manufacturer of the active substance have been adequately described.
An HPLC method is used by the AIM for assay and related substances. Satisfactory system suitability parameters have been established. The method has been validated in line with ICH and is claimed to offer better separation than the USP method.

The microbiological methods used by the finished product manufacturer are consistent with the USP and Ph Eur methods.

3.4.3 Batch analyses

Batch data from the AIM and the finished product manufacturer have been provided for all batches of morphine sulfate (pentahydrate) supplied to the finished product manufacturer. Compliance with USP, PhEur and in-house tests has been demonstrated. Several batches have been tested by the finished product manufacturer against the Ph Eur monograph and fully comply with the requirements of the monograph.

The batch data are generally satisfactory. However, data provided show levels of related substances above the proposed specification limits. The applicant has stated that at the time of testing, specification limits for these impurities had not been established. Satisfactory certificates of analysis have been provided for several additional lots that demonstrate that further batches of morphine sulfate pentahydrate will comply with the proposed specifications for related substances.

3.4.4 Justification of specification

The applicant has provided an adequate justification for the proposed specification.

3.5 REFERENCE STANDARDS OR MATERIALS

The USP reference standard has been established as the primary reference standard. This does not conflict with the Ph Eur monograph. A copy of the IR spectrum has been provided. The AIM certifies a secondary standard against the primary standard for use in the assay and related substances method. A satisfactory Certificate of Analysis has been provided for the current batch of secondary standard. All testing performed by the finished product manufacturer or the contract analytical laboratory uses USP Morphine Sulfate Reference Standard.

3.6 CONTAINER CLOSURE SYSTEM

Batches of active substance are stored double-wrapped in LDPE bags in HDPE drums. Satisfactory specifications have been provided for the above packaging components.

3.7 STABILITY

3.7.1 Stability summary and conclusions

The Ph Eur monograph requires that batches of the active substance are stored protected from light. Morphine salts are susceptible to oxidation with the main
products formed being pseudomorphine and morphine N-oxide.

Details of stress studies have been provided.

Stability data have been provided by the AIM for batches of active substance manufactured at the proposed site, stored in containers representative of the market container.

Stability data have been presented for batches stored under long-term and accelerated conditions. Furthermore, the AIM commits per the stability protocol to place at least one annual production lot on long-term controlled room temperature storage stability in a container/closure system representative of the market container. This is considered adequate.

Analytical methods were as used for routine batch release.

The active substance manufacturer has proposed a re-test period of 36 months based on the data provided. In addition, the finished product manufacturer will re-test any batches older than 36 months on an annual basis for conformance with specifications, up to a maximum period of storage of 5 years.

3.7.2 Post-approval stability protocol and stability commitment

A commitment has been provided that one commercial lot will be included in the stability programme each year.

4. MEDICINAL PRODUCT

4.1 DESCRIPTION AND COMPOSITION OF THE MEDICINAL PRODUCT

The product is presented as a sterile, non-pyrogenic, white to off-white aqueous suspension of multivesicular lipid-based particles containing morphine sulfate pentahydrate designed for epidural administration. Qualitative composition is described in Table 1. All three products are manufactured to the same % composition, but filled to different target volumes (1ml, 1.5ml and 2ml).

Table 1: Composition and function of ingredients

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Function</th>
<th>Reference Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine Sulfate (pentahydrate)</td>
<td>Active substance</td>
<td>Ph Eur/USP</td>
</tr>
<tr>
<td>Dioleoylphosphatidylcholine (DOPC)</td>
<td>Phospholipid component of lipid bilayer</td>
<td>HSE</td>
</tr>
<tr>
<td>Dipalmitoylphosphatidylglycerol (DPPG)</td>
<td>Phospholipid component of lipid bilayer /</td>
<td>HSE</td>
</tr>
<tr>
<td></td>
<td>anti-aggregant</td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>Stabilisation of lipid bilayer</td>
<td>Ph Eur/NF</td>
</tr>
<tr>
<td>Triolein</td>
<td>Stabilisation of lipid bilayer</td>
<td>HSE</td>
</tr>
<tr>
<td>Tricaprylin</td>
<td>Stabilisation of lipid bilayer</td>
<td>HSE</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>Tonicity adjustment</td>
<td>Ph Eur/USP</td>
</tr>
<tr>
<td>Diluted (10%) hydrochloric acid</td>
<td>pH adjustment</td>
<td>Ph Eur/NF</td>
</tr>
<tr>
<td>Water for injections</td>
<td>Intraparticular and external phase medium</td>
<td>Ph Eur/USP</td>
</tr>
<tr>
<td>Nitrogen</td>
<td>Headspace</td>
<td>Ph Eur/NF</td>
</tr>
</tbody>
</table>
No Genetically Modified Organisms are included in the products.

4.2 PHARMACEUTICAL DEVELOPMENT

4.2.1 Components of the drug product

The function of each ingredient included in the product has been described. No specific excipient-active compatibility studies have been conducted. Instead, absence of incompatibility is deduced from the stability studies conducted with the finished product.

4.2.2 Formulation development

A copy of the development report has been provided. This is satisfactory.

The product consists of multivesicular liposomes (MVL) in an aqueous suspending vehicle. The active substance is fully dissolved in the internal aqueous phase of the liposomes and is fully soluble throughout the manufacturing process. Structure has been shown by scanning electronmicrographs and use of confocal microscopy.

Sustained-release is achieved through the use of a combination of lipids that form the walls of the MVL particles. The major constituent of the lipid membrane is the zwitterionic phospholipid, dioleoylphosphatidylcholine (DOPC).

Selection of specific lipid components and their levels was based on a cytarabine product authorised in the EU through the Centralised Procedure (DepoCyte® 50mg Suspension for Injection), with refinement based on optimisation studies.

Morphine has reasonable aqueous stability and hence this was not a major concern during product development.

Compatibility has been shown between the product (undiluted and diluted 1:10 with normal saline and with Lactated Ringer’s) and several brands of catheter under conditions of ambient temperature and light. Due to the size of the MVLs the product cannot be passed through a 0.22µm in-line filter immediately prior to administration. This fact is highlighted in the SPC.

Lidocaine is often used in epidural administration protocols. Incompatibility of the MVL with lidocaine has been found resulting in a 1:1 exchange reaction in the MVLs of lidocaine for morphine. The SPC therefore includes details of a procedure that involves flushing the epidural catheter with saline following administration of lidocaine, followed by a 10-15 minute wait prior to administration of Depodur; this procedure avoids the above incompatibility reaction.

4.2.3 Physicochemical and biological properties

Particle size distribution of the MVL has been studied. The applicant has provided particle size profiles for scale-up trials that confirm that the manufacturing process is robust with respect to particle size distribution.
The surface charge on the MVLs prevents aggregation and allows resuspension on gentle swirling.

An in vitro model has been developed to characterise the release properties of the product. The method is used as a QC tool to monitor reproducibility of the manufacturing process.

4.2.4 Manufacturing process development

Process development and characterisation work including identification and optimisation of critical parameters was largely conducted at a small scale. The process was scaled-up and optimised. This is the intended initial commercial production scale and consistent with the scale used for manufacture of Phase III supplies. Details of the scale-up studies and in-process characterisation studies have been presented. A comparison has also been presented of the equipment and processing properties used for manufacture of both batch sizes. Batches produced at the two batch sizes are considered to be physicochemically equivalent.

4.2.5 Container and closure system

The applicant has provided a satisfactory rationale for the intended container/closure system. Evidence of the seal integrity of the container/closure system has been provided following immersion of vials containing growth medium in a bacterial suspension.

4.3 MANUFACTURE

4.3.1 Manufacturer(s)

Details of the proposed manufacturing sites and an alternative labelling and packaging site have been provided. Appropriate GMP documentation has been supplied.

The product will be released at Pharmaceutical Development and Manufacturing Services Limited, Seagoe Industrial Estate, Craigavon, Co. Armagh, Northern Ireland, UK under Manufacturing Authorisation Number ML/20166/1. A copy of the current Manufacturing Authorisation issued by the MHRA has been provided for the batch release site.

4.3.2 Batch formula

A formula has been provided for the manufacture of the proposed maximum batch size.

4.3.3 Description of manufacturing process and process controls

A flow chart of the manufacturing process has been provided.

4.3.4 Control of critical steps and intermediates
Critical steps have been identified and satisfactory in-process controls applied. The acceptance criteria for the in-process controls applied during the manufacturing process have been described and are acceptable.

4.3.5 Process validation and/or evaluation

The manufacturing process has been validated at full scale.

The applicant has provided a commitment that the manufacturing process will be further validated through a prospective validation study and a satisfactory protocol was provided.

4.4 CONTROL OF EXCIPIENTS

4.4.1 Specifications

All ingredients comply with relevant Ph Eur, BP, DAB, USP or NF monographs with the exception of DOPC, DPPG, triolein and tricaprylin, that in the absence of pharmacopoeial monographs, are controlled to in-house specifications. Sodium chloride and processing aids are also subject to microbial and bacterial endotoxin testing. Satisfactory acceptance criteria have been set.

DOPC, DPPG and triolein are included in DepoCyte Injection containing cytarabine (EM 20334/0001). Tricaprylin (glyceryl tricaprylate, caprylic acid triglyceride, CAS No. 538-23-8) appears to be a new excipient for UK products. It is therefore necessary that detailed information is included in the dossier on the manufacture and control of this excipient. Satisfactory data have been provided. A short entry is included in Martindale in which it is stated that tricaprylin has the general properties of the medium-chain triglycerides. Glyceryl monocaprylate is included in products authorised in the UK.

A vendor qualification programme is in place consisting of full testing on the first three batches from a specific vendor with results compared with the Certificate of Analysis from the supplier. If the results are acceptable and supported by a satisfactory GMP inspection, reduced testing may be performed. One batch will be fully tested each year. Satisfactory specifications for DOPC, DPPG, triolein and tricaprylin have been provided. Satisfactory Certificates of Analysis and analytical methods have been provided for the above ingredients.

The applicant has provided an acceptable response to justify absence of testing for microbial quality for DOPC, DPPG, triolein and tricaprylin.

Information has been provided on nomenclature, structure, manufacturing process, control measures, impurities, characterisation and stability for triolein, tricaprylin, DOPC and DPPG.

4.4.2 Excipients of human or animal origin
The MAA forms indicate that cholesterol is the only material of animal or human origin contained in or used in the manufacturing process for the proposed products. It is prepared from sheep and is not derived from specified risk materials as defined in Commission Decision 97/534/EC.

Satisfactory TSE declarations have been provided from the suppliers of the cholesterol.

4.5 CONTROL OF MEDICINAL PRODUCT

4.5.1 Specification

The proposed finished product specification has been supplied.

Batches of finished product are tested in the US (where the product is manufactured) to the specification described. The applicant has proposed slightly reduced testing on import. It is proposed that the tests for particle size, osmolality, process residuals, uniformity of dosage units, deliverable mass or volume, bacterial endotoxins and sterility are not repeated on import. The applicant has provided individual justifications for omitting each of these tests. The basis for this is that each parameter cannot increase during storage. It is also stated that where these tests are not performed on re-testing on import, the results of testing in the US should be available to the QP responsible for batch release on the Certificate of Analysis for the batch. In accordance with Article 51 of Directive 2001/83/EC, the holder of the marketing authorisation has a responsibility to ensure that each production batch from a ‘third country’ has undergone in the importing Member State, a full qualitative analysis, a quantitative analysis of at least all the active constituents and all the other tests or checks necessary to ensure the quality of the medicinal product in accordance with the requirements of the marketing authorisation. Given the above requirements, the above proposal is accepted in this specific case.

With respect to the limits applied on re-testing on import, the shelf life limits are applied. This is acceptable.

4.5.2 Analytical procedures / Validation of analytical procedures

Details have been provided of the analytical methods used.

Identity and total morphine sulfate concentration are determined by an HPLC method. The same HPLC method is used to quantify the free morphine content following separation of the MVL-entrapped morphine sulfate. This method is also used for content uniformity in accordance with Ph Eur 2.9.6. The method has been validated in accordance with ICH requirements.

A second method is used for identification (colour reaction).

Morphine related substances are determined by an HPLC method. The method has been validated in accordance with ICH requirements.

A number of HPLC methods are used in the identification of DOPC, DPPG,
triolein, tricaprylin, Lyso-DOPC and cholesterol. The presence of sodium and chloride are confirmed using the methods described in the Ph Eur. The methods enabling quantitation of DOPC, DPPG, cholesterol, triolein, Lyso-DOPC and tricaprylin have been validated in accordance with ICH requirements.

Particle size distribution is by laser light scattering. Satisfactory results for the verification of accuracy and precision have been presented for the method.

In vitro release is performed to monitor batch to batch variation. The method has been validated in accordance with ICH requirements.

GC, Free Solution Capillary Electrophoresis (FSCE) and HPLC methods are used to determine process residuals. All methods have been validated in accordance with ICH requirements.

Levels of particulate matter are tested in accordance with Ph Eur 2.9.19 following dissolution of the product in 80% isopropanol (005-10030).

Bacterial endotoxins are determined using the USP (Ph Eur equivalent) LAL gel clot method. The method has been validated.

The test for sterility is performed in accordance with USP <71> with samples dissolved in sterile diluent Fluid D. The method is suitable and has been validated.

4.5.3 Batch analyses

Batch analysis data have been provided for commercial scale batches manufactured between July 2000 and January 2003, and pilot scale batches manufactured between May 1996 and March 2000. Batches used in clinical and pre-clinical studies are included. All batches have been manufactured at the proposed commercial manufacturing site. Most of the test parameters for the above batches comply with the proposed specifications, although data using the recently-developed methods for morphine-related substances and lyso-DOPC are limited to the commercial scale batches; ‘initial’ data for these parameters were obtained from samples frozen at -70°C. The values for morphine content for two batches were out of specification however the applicant has stated that this was due to the limits being tightened after these batches had been manufactured. This is acceptable. One batch is reported as failing the test for sterility. An investigation was carried out and the summary is accepted as is the conclusion that no cause could be assigned. The batch was rejected.

4.5.4 Characterisation of impurities

Potential impurities in the product arising from morphine sulfate have been named. Of these potential impurities, only pseudomorphine has been observed as a degradation product in the finished product. As a consequence, the specification includes a specific limit for pseudomorphine and for total other morphine-related substances. The limit for other total morphine-related substances is acceptable given
the control of individual substances in the active substance specification.

Potential degradation products arising from the lipid components have been named. The applicant has supplied a suitable justification for the absence of limits for these substances in the finished product specification. Process-related impurities have also been named.

4.5.5 Justification of specifications

A satisfactory justification for the release and shelf-life limits has been provided. Acceptance criteria have generally been set with consideration to industry/compendial standards, the specific batches used in clinical studies and production experience during product development.

The limit for free morphine is well below the typical bolus 5mg dose of morphine administered by the epidural route in conventional aqueous solutions.

The acceptance criteria for lyso-DOPC is acceptable given that studies reported in the literature have found that up to 15% hydrolytic decomposition of phospholipids to lysophospholipids does not significantly alter bilayer permeability.

The proposed acceptance criteria for the other defined parameters are justified by ICH guidelines and/or by batch and stability data.

4.6 REFERENCE STANDARDS OR MATERIALS

The following compendial reference standards are used:

- USP Morphine Sulfate RS
- USP Dextrose RS
- Ph Eur Cholesterol CRS
- USP Endotoxin RS

Secondary standards for the above compendial standards may be used after appropriate characterisation and qualification (minimum of identity, assay and HPLC purity).

Certificates of Analysis and supporting spectra have been provided for non-compendial reference standards.

4.7 CONTAINER-CLOSURE SYSTEM

The products are presented in 2ml Type I amber glass vials with ethylenetetrafluoroethylene (ETFE)-coated stoppers and aluminium caps. Product presentations are differentiated by the colour of the plastic seal cap.

Satisfactory specifications, drawings and methods have been provided for the packaging components. Identity of the rubber stoppers is confirmed by IR on receipt. The vials comply with the Ph Eur requirements for Type I glass and with the Ph Eur requirements for surface hydrolytic resistance, arsenic and light transmission. The stoppers conform to the Ph Eur requirements for Rubber Closures
4.8 STABILITY

4.8.1 Stability summary and conclusion

Stability data were generated for commercial-scale batches of 20mg/2ml and 10mg/1ml product. All batches were manufactured at the proposed commercial manufacturing site. All batches were filled into 2ml amber Type I glass vials and sealed with rubber stopper and seal as intended in the proposed commercial packs. Supporting data are also included on pilot-scale batches.

The analytical methods used were as described for routine batch release, except for the method for particle size control.

Stability data provided: 5 ± 3°C, 8 ± 2°C, 25 ± 2°C, 37 ± 2°C, photostability studies, freeze-thaw

Test parameters: All studies: appearance, total morphine, free morphine, particle size, pH, in vitro release, bacterial endotoxins, sterility
Some studies: morphine related substances, lyso-DOPC, DOPC, DPPG, cholesterol, triolein, caprylin
Only morphine content and free morphine were determined at 37°C
Photostability in clear vials, amber vials and wrapped in foil
Freeze-thaw study, temperature cycling 5°C/25°C, ambient temperature/light study

At the recommended storage conditions (2-8°C) or at the slightly higher conditions of 8 ± 2°C there was essentially no change in total morphine content or morphine degradants after storage. There was no apparent change in lipid content and only a small increase in lyso-DOPC. There was a slight reduction in particle size and a slight drift in pH. The % free morphine increased steadily over time.

Samples stored at 25°C showed greater leakage (% free morphine) and a reduction in pH. Other parameters were much as reported for the 2-8°C and 8 ± 2°C conditions.

At 37°C there was virtually no change in total morphine although the rate of morphine leakage increased. Changes were also seen in pH, particle size in vitro release profile, morphine-related substances and in lyso-DOPC content.

Similar observations were seen in the pilot scale batches.

No significant differences were seen between the results for vials stored inverted or upright.
The photostability studies showed sensitivity of the product when filled into clear vials (increase in pseudomorphine, reduction in morphine content, reduction in pH). The product packed in amber glass is protected from the effects of light.

It has been shown that the integrity of the MVL is lost on freezing to -20°C leading to a significant increase in free morphine and a drop in pH. The SPC, leaflet and labelling state the storage condition, ‘do not freeze’.

It was found that temperature cycling had no effect on total morphine, free morphine or on in vitro release.

Satisfactory container integrity tests have been conducted. No visual signs of growth occurred in the vials, during the test period.

The key parameter that is stability-limiting is the free morphine content. Increase in free morphine appears to follow zero-order kinetics. Samples stored at 2-8°C and at 8 ± 2°C remained within specification after 2 years storage.

The applicant has proposed a shelf-life of 2 years for product carrying the storage recommendations ‘Store at 2-8°C’ and ‘Do not freeze’. The proposed storage conditions and shelf life are acceptable.

4.8.2 Post-approval stability protocol and stability commitment

A commitment has been provided that the first 3 commercial batches will be placed on stability. At least one batch will be added to the stability programme each year. Batches will be tested according to the protocol provided in the dossier for up to 24 months.

The applicant has also provided a commitment to initiate stability studies with a further 2 batches of the 10mg/1ml presentation filled into 2ml vials.

4.9 BIOEQUIVALENCE/BIOAVAILABILITY

During the clinical studies, pharmacokinetic data were analysed for 282 subjects and patients. It is reported that pharmacokinetics were linear and roughly dose-proportional (based on AUC) across the range 5-30mg. \( C_{\text{max}} \) was not always dose-proportional and tended to increase by an amount less than the proportional change in dose. In females, a 25% increase in \( C_{\text{max}} \) was observed compared to males. As no difference in safety or efficacy was seen as an effect of gender it has been concluded that the difference in \( C_{\text{max}} \) is not of clinical relevance.

As the product will be used as a single dose there is no opportunity for accumulation of morphine sulfate or its metabolites and so no dose adjustment is necessary in patients with impaired hepatic or renal function.

5. MAA FORM

The MAA forms are satisfactory.
6. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The SPCs are satisfactory.

7. LABELLING

The labelling is satisfactory.

8. PATIENT INFORMATION LEAFLET

The leaflets are satisfactory.

9. STATEMENT ABOUT THE AUTHOR OF THE OVERALL QUALITY SUMMARY

The Expert for the report on Quality is a chemist. The Expert is suitably qualified and has relevant experience.

10. CONCLUSIONS

The source of active substance is known and is used in products already authorised in the UK. The Drug Master File (DMF) has been updated.

Development of the MVL has been described and there are no objections to the ingredients used in manufacture of the product for epidural use.

Stability data have been provided that support a shelf life of 2 years when store at 2-8°C.

There is no requirement for a bioequivalence study.

Note regarding consideration by Chemistry, Pharmacy and Standards Subcommittee:
This application was presented to the Chemistry, Pharmacy and Standards Subcommittee on 01/10/1998. The committee considered that the licences could be granted providing a number of points were resolved.

From a pharmaceutical point of view, these Marketing Authorisations may be granted.
INTRODUCTION

This is a National application under Directive 2001/83/EEC Article 10a [formerly 10.1(a)(ii)].

DepoMorphine, also known as SKY0401, consists of lipid-based particles (DepoFoam™) containing the active ingredient. The particles are suspended in 0.9% saline. Since the properties of morphine are well established, the nonclinical programme focuses on demonstrating that morphine is actually released from DepoFoam™ and that DepoFoam™ – naturally occurring materials or analogues of them - is likely to be safe when used for epidural injection.

The proposed indication is for the relief of post-operative pain for up to 48 hours and the proposed maximum dose is 20mg.

Scientific Advice was sought from several regulatory authorities prior to this submission. Those that considered nonclinical issues were FDA, CPMP, Irish Medicines Board and MHRA. There were no findings that could not have been predicted from the already well-established properties of morphine.

I.1 GLP aspects

With the exception of an epidural injection bioequivalence study in dogs, all toxicity studies were conducted to GLP.

II. PHARMACODYNAMICS

All pharmacodynamic studies were conducted in dogs. Doses of 10 and/or 30mg SKY0401 were investigated and compared with 5mg unencapsulated morphine. The epidural, intravenous and intrathecal routes of administration were used.

In addition to standard clinical observations, the following parameters were quantified:

- antinociceptive response (thermal-evoked skin twitch)
- behaviour (arousal, muscle tone, co-ordination)
- physiological effects (temperature, heartrate, respiratory rate, blood pressure)

II.1 Pharmacodynamics for the Proposed Indications

The transient antinociceptive, behavioural and physiological effects of SKY0401 were similar to those of unencapsulated morphine.
Both intravenous morphine and SKY0401 administration resulted in a complete block of the skin twitch response with an onset of 5-60 minutes and duration of 6-10 hours. Compared with intravenous administration, the onset of skin twitch blockade was delayed after intrathecal or epidural administration of SKY0401 with the peak effect occurring after 3-6 hours and the duration extended to 24-48 hours. Overall, the findings are consistent with the slow release of the active ingredient from the DepoFoam™ matrix.

The death of one dog receiving 30mg SKY0401 by intrathecal administration was attributed to 'increasing neurological deficits' as the result of misplacement of the catheter. Since the other 3 dogs in this study survived without any long-term adverse effects this is probably the correct explanation.

II.2 Secondary Pharmacology

See above section.

II.3 SAFETY PHARMACOLOGY

Separate studies have not been conducted. Data on some aspects of Safety Pharmacology were generated in the pharmacodynamic studies (see II.I above).

II.4 Pharmacodynamic Drug Interactions

Studies not conducted.

II.5 Assessor’s Comment

The applicant has convincingly demonstrated that SKY0401 has similar pharmacodynamic properties to unencapsulated morphine and is therefore likely to be efficacious in the proposed indication.

III. PHARMACOKINETICS

Pharmacokinetic studies were limited to measurements in dogs of absorption following single and repeated dosing by the epidural, intravenous and/or intrathecal routes. Drug-drug interaction studies with lidocaine were also conducted. Similar doses to those in the pharmacodynamic studies were administered.

III.1 Methods of analysis

The majority of assays utilised a commercially available RIA kit (Coat-A-Count®) with LOQ of 2.5ng/ml. In one instance, an HPLC/MS method was used with LOQ 5ng/ml.
III.2  Absorption

The following were established:

- morphine is released slowly and completely from SKY0401
- bioequivalence between pilot and commercial scale preparations was not conclusively demonstrated with the 90% confidence intervals for $C_{\text{max}}$ and AUC failing to meet current criteria
- morphine did not accumulate in plasma or CSF
- differences in serum concentrations between males and females were attributed to weight differences
- co-administration with lidocaine resulted in faster release of morphine but this could be obviated by a 15 minute gap between the two administrations

Typical systemic AUC values after bolus epidural administration of morphine sulphate solution were 2-3 orders of magnitude greater than the mean AUC of 39ng.h/ml in patients following administration of 5mg Depodur. $C_{\text{max}}$ was also greater than clinical values of 7ng/ml but by less than an order of magnitude.

It has been assumed by the applicant that the lipids which constitute DepoFoam™ are remodelled, incorporated, metabolised and/or cleared in a similar manner to endogenous lipids.

III.3  Distribution

Studies not conducted.

III.4  Metabolism

Studies not conducted.

III.5  Excretion

Studies not conducted.

III.6  Toxicokinetics

Studies not conducted.

III.7  Assessor’s Comment

The presence of morphine in plasma and CSF has been satisfactorily quantified. Thereafter, the other pharmacokinetic properties can be assumed to have been already characterised in previous submissions and by extensive clinical use.
The failure to demonstrate bioequivalence between pilot and commercial batches is disappointing but not crucial. With only 6 dogs in the crossover study it was almost inevitable that the not almost predictable observation of inter-animal variation would have a significant effect.

The assumptions relating to the lipid constituents of DepoFoam™ are reasonable.

IV. TOXICOLOGY

The dog was again the species used in these studies. The maximum dose (30mg) was restricted by the solubility limit of SKY0401 (10mg morphine/ml) and the maximum tolerated dose volume (3ml).

The epidural, intravenous and intrathecal routes of administration were investigated.

IV.1 Single Dose Toxicity Studies
Evidence of toxicity was effectively limited to adverse clinical signs consistent with high-dose pharmacological activity and inflammation at the point of insertion of the catheter.

IV.2 Repeated Dose Toxicity Studies
There were no additional signs of toxicity following repeated weekly dosing and no histopathological findings of clinical significance.

IV.3 Genotoxicity Studies
A very brief literature review of the genotoxicity of morphine is contained in the NonClinical Overview.

IV.4 Carcinogenicity Studies
Studies not conducted.

IV.5 Reproductive and developmental toxicity
A very brief literature review of the reprotoxicity of morphine is contained in the NonClinical Overview.

IV.6 Local tolerance and sensitization
Studies not conducted.

IV.7 Other toxicity studies

IV.7.1 Antigenicity
Studies not conducted.
IV.7.2 Immunotoxicity

Studies not conducted.

IV.7.3 Dependence

Studies not conducted.

IV.7.4 Studies on impurities

The impurity profile of batches of morphine sulphate used in SKY0401 development and their use in nonclinical studies have been provided. There are no clinical concerns in this respect.

IV.8 Ecotoxicity/environmental risk

The PEC_{water} for SKY0401 is calculated to be $9 \times 10^{-9} \mu g/ml$. There are, therefore, no concerns relating to environmental toxicity.

IV.9 Assessor’s overall conclusions on toxicology

The limited programme of toxicity studies is suitable for a product intended for single administration. There were no unanticipated findings and none of clinical concern.

The NonClinical Expert provides a brief review of studies on DepoFoam™ alone in several species. There are no findings of potential clinical significance.

V. NONCLINICAL OVERVIEW

This was written by a qualified pharmaco-toxicologist. It is satisfactory.

VI. CONCLUSION

There are no nonclinical objections to the grant of a Product Licence.

Summary of Product Characteristics

The SPC is satisfactory.
CLINICAL ASSESSMENT

NOTE: This clinical assessment report has been put together “chronologically”. The assessment includes queries raised by the assessor (in italics) and considered by the UK Advisory Committee. The assessment of the company’s response to the queries is presented below, in the section of this report concerning the Committee’s recommendations.

I. INTRODUCTION

This is a bibliographic National application under Directive 2001/83/EEC Article 10(a) [formerly article 10.1(a)(ii)] for a lipid-based modified release Morphine Sulfate (MS) preparation for epidural administration for the relief of post-operative pain for up to 48 hours.

Depodur, known during development as SKY0401, is a sterile aqueous suspension of multivesicular lipid-based particles (DepoFoam drug delivery system) containing the active ingredient morphine sulfate 10mg/ml. It is intended for local sustained release following a single epidural administration prior to the initiation of surgery, in order to achieve post-operative analgesia for up to 48 hours. The applicant proposes presentation in 1ml, 1.5ml and 2ml single use ampoules.

The bibliographic data are heavily supported by original clinical trial data. Since the properties of morphine are well established, the clinical development programme focuses on demonstrating the safety and effectiveness of the new product Depodur given as a single epidural injection for the relief of post-operative pain.

A pending CPMP guideline on the investigation of nociceptive pain is currently undergoing public consultation.

Scientific Advice was sought from several regulatory authorities prior to this submission, including the FDA, CPMP, and MHRA.
I.1 GCP aspects

The clinical expert confirms that all submitted studies for Depodur are GCP compliant.

I.2 Orphan Medicinal Products

Not applicable.

I.3 Therapeutic Class

Pharmacotherapeutic group: Natural opium alkaloid
ATC Code: N02A 01

I.4 Background

Depodur is a sustained-release formulation of the active ingredient morphine sulfate designed for epidural administration. Morphine released from Depodur is absorbed both systemically and neuraxially. It reaches its principal site of action via transfer across the meninges and intrathecal space into the dorsal spinal cord. Post-operative administration of epidural opioids including morphine is a well established technique providing high quality analgesia of long duration without loss of motor, sensory, or sympathetic function. The purpose of this product is to achieve up to 48 hours of analgesia of following a single injection, avoiding the disadvantages associated with epidural infusion or repeated boluses both of which necessitate leaving a catheter in situ. For practical reasons not all surgical wards can manage epidural catheters and/or infusions, and rare complications such as epidural abscesses and haematomas can be devastating.

I.5 Regulatory Status

This is the first application for Depodur within the EU.

I.6 Indications

For the relief of post-operative pain for up to 48 hours.
I.7 Dose and Dose Regimen

Adults and the elderly
Depodur is intended only for epidural administration. Intravenous, intramuscular and intrathecal administration are contraindicated. Depodur may be administered perioperatively via needle or catheter at the lumbar and lower thoracic levels, except in caesarean section (see below). Administration of Depodur at the mid-thoracic level or higher has not been studied. Depodur may be administered undiluted or may be diluted up to 5ml total volume with preservative-free 0.9% normal saline.

Table 1: Dosing Recommendations by Surgery Type and Patient Age

<table>
<thead>
<tr>
<th>Surgical Populations</th>
<th>Age categories</th>
<th>&lt; 65 years</th>
<th>≥ 65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip and knee orthopaedic</td>
<td>20mg</td>
<td></td>
<td>15mg</td>
</tr>
<tr>
<td>Lower abdominal</td>
<td>20mg</td>
<td></td>
<td>15mg</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>10mg</td>
<td></td>
<td>N/A</td>
</tr>
</tbody>
</table>

Depodur has been administered to women undergoing caesarean section following clamping of the umbilical cord. Depodur should not be administered to women for vaginal labour and delivery.

Depodur should be administered by or under the direction of a physician experienced in the technique of epidural administration and who is thoroughly familiar with the labelling of this product.

Improper placement of a needle or catheter in the epidural space should be ruled out before Depodur is injected. Acceptable techniques to rule out improper placement of a needle or catheter include: a) aspiration to check for absence of blood or cerebrospinal fluid and/or b) administration of 3ml of 1.5% preservative-free lidocaine and adrenaline (1:200,000) test dose. If a test dose is administered, observe the patient for lack of tachycardia (this indicates that vascular injection has not occurred) and lack of segmental anaesthesia (this indicates that intrathecal administration has not occurred). To minimise a pharmacokinetic interaction of Depodur with the test dose, flush the catheter/needle with 1ml of preservative-free 0.9% normal saline and wait for at least 10 minutes after administration of the test dose before administering Depodur.

Do not mix Depodur with any other medications. Once Depodur has been administered, no other medication should be administered into the epidural space for at least 48 hours.

Do not use an in-line filter during administration of Depodur.

Depodur is a sterile agent; however, it does not contain any bacteriostatic agents. Therefore, Depodur must be administered within 4 hours after withdrawal from the vial. Do not heat-sterilise or gas-sterilise.

Discard any unused portion in a manner appropriate for opioids.
Protect Depodur from freezing. Do not administer Depodur if it is suspected that the vial has been frozen.

Paediatrics
The safety and effectiveness of Depodur in paediatric patients below the age of 18 years has not yet been established.

I.8 Consideration for Paediatric use

The applicant has provided an undertaking to develop the product for use in children following approval of the indication in adults. Paediatric studies with lumbar epidurals are not planned. Caudal epidural block using local anaesthetics (e.g. bupivacaine) with or without opioids is frequently used in combination with general anaesthesia in the paediatric population undergoing surgical procedures of the lower part of the body to facilitate post-operative pain management.

I.9 Information on the bibliographic dossier

The applicant has provided justification of the bibliographic legal basis of this application, including full tabulation of existing Marketing Authorisations, and detailed information on the literature search performed. A comprehensive review of this literature is provided.

I.10 Assessor's Comment

The requirements of a bibliographic application for a drug substance that has been widely used off label over a considerable period of time are essentially the same as for a new drug. The company has done a generally good job of conducting a full literature search and review, along with all of the regulatory requirements such as provision of tabulated study synopses. However a number of the cited references are available on request. They should be submitted unless otherwise justified.
II. CLINICAL PHARMACOLOGY

II.1 Pharmacokinetics

II.1.1 Introduction

The pharmacokinetic (PK) profile of Morphine Sulfate (MS) administered both systemically and epidurally in aqueous solution is reasonably well characterised in the literature. Section 5.2 of the proposed SPC for Depodur provides the following information:

Epidural administration of Depodur results in both systemic absorption of morphine sulfate and absorption of morphine sulfate through the meninges into the intrathecal space. The relative absorption systemically versus intrathecally is unknown for both morphine sulfate injection and for Depodur.

Systemic Absorption of Morphine from Depodur
Relative systemic bioavailability of Depodur compared to epidurally administered morphine sulfate injection was determined in 21 patients (Table 2).

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Depodur 5mg (n = 10)</th>
<th>Morphine sulfate Injection 5mg (N = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>7.10</td>
<td>3.40</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (hr)$^1$</td>
<td>1.00</td>
<td>(0.25 – 4.0)</td>
</tr>
<tr>
<td>AUC (ng.hr/ml)</td>
<td>38.80</td>
<td>10.35</td>
</tr>
<tr>
<td>$t_{1/2}$ (hr)</td>
<td>3.82</td>
<td>1.00</td>
</tr>
<tr>
<td>AUC$^2$</td>
<td>37.41</td>
<td>43.48</td>
</tr>
</tbody>
</table>

$^1$ Median (range)

$^2$ Geometric mean of the log-transformed variable used to calculate bioavailability

Depodur was 89% bioavailable compared to morphine sulfate injection and demonstrated dose proportionality over a dose range of 5 to 25mg.

Distribution, Metabolism and Excretion of Morphine Sulfate
After morphine sulfate has been released from Depodur and is absorbed systemically, its distribution, metabolism and excretion are the same as other morphine formulations. Depodur is intended for single dose administration; therefore accumulation of morphine or its metabolites is not expected even in patients with impaired hepatic or renal function.

The bibliographic references submitted in the dossier largely focus on the pharmacokinetics of aqueous epidural morphine. They are sufficient for this purpose. In addition the applicant has presented a package of pharmacokinetic studies characterising the pharmacokinetics of the Depodur formulation. Data on morphine and its two principal glucuronide metabolites were generated by studies DTC96-003, C0401-008, C0401-009, SKY0401-011, SKY0401-012B, and SKY0401-016. In addition the effects of lidocaine/adrenaline test dose administration on the PK profile of SKY0401 was investigated in study SKY0401-016.
II.1.2  Systemic absorption and plasma concentration - time profile

Study SKY0401-012B

This Phase III clinical study comparing Depodur to a comparator aqueous morphine formulation included a pharmacokinetic sub-study. Following epidural administration, blood samples for determination of morphine, morphine-3-glucuronide, and morphine-6-glucuronide plasma concentrations were taken at 0, 0.25, 0.5, 1, 2, 4, 8, 12, 18, 24, 36 and 48 hours after dose administration. Plasma concentration data from subjects receiving Duramorph 5mg and Depodur 5mg are presented both graphically and in tabular for below. Note that Cmax of 10mg orally of a morphine solution is 20ng/ml.

Average Morphine Plasma Concentrations in Study SKY0401-012B (n = 8 per treatment group)

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Duramorph 5 mg (N = 8)</th>
<th>SKY0401 5 mg (N = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/ml)</td>
<td>7.22</td>
<td>19.90</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>1.00</td>
<td>0.25</td>
</tr>
<tr>
<td>AUC0-T (ng•hr/ml)</td>
<td>32.81</td>
<td>35.52</td>
</tr>
<tr>
<td>AUCinf (ng•hr/ml)</td>
<td>37.29</td>
<td>39.45</td>
</tr>
<tr>
<td>Ke (hr⁻¹)</td>
<td>0.1894</td>
<td>0.3095</td>
</tr>
<tr>
<td>T½ (hr)</td>
<td>3.92</td>
<td>3.03</td>
</tr>
</tbody>
</table>

Assessor’s comment
The attenuated peak in systemic exposure for Depodur is consistent with its claimed modified release characteristics. Systemic bioavailability is 90% of that of Duramorph, indicating no evidence of sequestration. It is not necessary to show “bioequivalence”. The plasma levels following Depodur 5mg are barely therapeutic for a systemic effect but for a 20mg dose would be well into the systemic therapeutic range. Full characterisation of the
plasma concentration – time curve is required for the 20mg dose and in comparison with oral and intravenous administration.

II.1.3 CSF drug levels

In Phase 1 CSF and plasma were assessed in a small number of healthy volunteers and showed that CSF morphine levels were approximately 150-fold higher than plasma morphine levels. In the Phase 2 and 3 studies only plasma morphine levels were measured, with no further sampling of CSF morphine levels, as morphine CSF levels. The company argues not only that it is not practical or ethical to perform repeated lumbar punctures in these peri-operative patients, but also that morphine CSF levels have not been shown to closely correlate with safety or efficacy parameters for unencapsulated morphine.

The applicant argues that higher epidural doses can be administered as Depodur than as unencapsulated morphine without the $C_{\text{max}}$ rising to potentially systemically toxic levels. This is true for systemic levels and those side effects mediated by systemic drug levels. However there is a lack of human data on CSF levels to support this claim. In particular late respiratory depression is believed to result from circulation of opioid to the brainstem via the CSF (early respiratory depression by contrast primarily reflects systemic drug levels).

Assessor’s comment

Very little information is available on CSF levels in humans. Demonstration of the depot effect of Depodur in the epidural space compared with unencapsulated morphine therefore rests on preclinical data and on the markedly attenuated plasma $C_{\text{max}}$ and the markedly delayed $T_{\text{max}}$, shown in study SKY0401-012B. This is considered acceptable. Measurement in humans of drug levels from CSF in the region of the cervical spine or brainstem is not feasible and therefore answers to questions relating to the potential for late respiratory depression are likely to rely on animal data. Clinical data relating to this area of potential concern are considered in the section on safety.

II.1.4 Effect of lidocaine/adrenaline test dose on the PK profile - Study SKY0401-016

The effects of a test dose of lidocaine and adrenaline on the pharmacokinetic profile of a single epidural dose of Depodur was investigated in Study SKY0401-016. In this randomised, open-label, parallel-group trial, five clinical scenarios were tested as shown in the following table.

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment Regimen Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No test dose + SKY0401 15 mg + Flush</td>
</tr>
<tr>
<td>2</td>
<td>Test dose + Flush + 3 min wait + SKY0401 15 mg + Flush</td>
</tr>
<tr>
<td>3</td>
<td>Test dose + Flush + 10 min wait + SKY0401 15 mg + Flush</td>
</tr>
<tr>
<td>4</td>
<td>Test dose + Flush + 15 min wait + SKY0401 15 mg + Flush</td>
</tr>
<tr>
<td>5</td>
<td>Test dose + 3 min wait + SKY0401 15 mg + Flush</td>
</tr>
</tbody>
</table>
The mean AUCt of plasma morphine concentrations at 4 time points are presented below.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (0-0.5hr)</td>
<td>3.6</td>
<td>12</td>
<td>5.0</td>
<td>5.1</td>
<td>11</td>
</tr>
<tr>
<td>AUC (0-1hr)</td>
<td>7.4</td>
<td>22</td>
<td>11</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>AUC (0-2hr)</td>
<td>16</td>
<td>33</td>
<td>21</td>
<td>21</td>
<td>31</td>
</tr>
<tr>
<td>AUC (0-4hr)</td>
<td>37</td>
<td>47</td>
<td>38</td>
<td>37</td>
<td>52</td>
</tr>
</tbody>
</table>

[1] Percentage of morphine AUC measured during indicated time interval relative to AUC₀₋₄₅ (measured from time 0 to the last concentration > the limit of quantitation).

The lidocaine/adrenaline test dose resulted in an increase in the rate of systemic morphine absorption from an epidural dose of Depodur administered three minutes later, regardless of whether the catheter was flushed prior to injecting the Depodur. This effect persisted for approximately 2 hours but no differences in rate of absorption were apparent between 2 and 4 hours (AUC 2 - 4 hrs).

Flushing the catheter (group 5 vs. group 2) and waiting longer (10 or 15 minutes – groups 3 and 4 vs. group 2) significantly reduced the impact of the interaction.

The applicant proposes that the interaction with the test dose is due to an increased rate of morphine release from the liposomal matrix. The SPC states the following in section 4.2:

To minimise a pharmacokinetic interaction of Depodur with the test dose, flush the catheter/needle with 1ml of preservative-free 0.9% normal saline and wait for at least 10 minutes after administration of the test dose before administering Depodur.

And in section 4.5:

Local anaesthetics: Clinical studies have demonstrated that administration of Depodur three minutes after a 3ml test-dose (lidocaine 1.5% and adrenaline 1:200,000) increases peak serum concentrations of morphine. However, no clinically meaningful effects on safety or efficacy were observed, despite the administration of such a test dose. Increasing the interval between the test dose and Depodur administration to at least 10 minutes minimises this pharmacokinetic interaction. Please see the dosage recommendations in Section 4.2 in respect of this interaction.

Assessor’s comment
The data from this and other studies indicate that the mean plasma Cmax is increased by approximately 60% by a standard lidocaine and adrenaline test dose. This effect is reduced but not abolished by waiting for 10 minutes before administering Depodur. Flushing after the test dose with normal saline appears to have no effect (group 2 vs. group 5). The 10 minute wait probably allows much of the test dose to be cleared from the site of the subsequent injection of Depodur. It appears that this is likely to be due to a direct effect of local anaesthetics on the physical properties of the delivery system, resulting in premature drug release. This has important implications not just for a test dose but for epidural regional anaesthesia for the surgical procedure.
II.1.5 Interaction with therapeutic doses of epidural local anaesthetic

The clinical overview states that during development “it was discovered that lidocaine displaces MS out of DepoFoam particles in vitro and in vivo on a molar to molar basis, and a similar interaction is anticipated with all local anaesthetics”. Study SKY0401-016 appears to bear this out. This interaction is of great importance because in normal anaesthetic practice therapeutic doses of local anaesthetic are almost invariably administered when epidural opioids are given peri-operatively. It would be normal to inject up to 20ml of local anaesthetic via the epidural catheter prior to commencing surgery (including patients under General Anaesthesia) whilst the opioid might be given at the same time or at a later time in order to provide post-operative analgesia. It would be unusual to administer epidural opioids without any local anaesthetic.

The SPC gives the following advice:

*Do not mix Depodur with any other medications. Once Depodur has been administered, no other medication should be administered into the epidural space for at least 48 hours.*

And:

*Other than the interaction with a lidocaine plus adrenaline test-dose described above, no other pharmacokinetic drug-drug interactions have been examined in vivo. In vitro studies suggest a similar interaction could be expected with other amide local anaesthetics. No in vitro or in vivo studies have been performed with ester local anaesthetics.*

The SPC does not however advise against administration with local anaesthetics.

Following a meeting with the company at MHRA at which this issue was raised, the company has drawn up plans to conduct a clinical study to investigate the possible interaction with therapeutic doses of epidural local anaesthetic administered per-operatively. These data will not be available in the near future.

**Assessor’s comment**

The lack of information on the performance of the product is an important deficiency, especially since it has been shown that the small dose of local anaesthetic used as a test dose causes a clinically relevant increase in the rate of morphine release from the liposomal matrix. There are insufficient human data to exclude the possibility that the volumes of local anaesthetic used for epidural anaesthesia or augmentation of General Anaesthesia might cause a serious failure of the modified release mechanism. As the total dose of morphine given as a single bolus of Depodur is much higher than the safe dose of unencapsulated epidural morphine, this could have major safety implications. *At the very least co-administration with therapeutic doses of epidural local anaesthetic should be contraindicated.* This would substantially limit the usefulness of the product.
II.1.6 Interaction with 0.9% normal saline used for dilution of Depodur

The SPC states that “Depodur may be administered undiluted or may be diluted up to 5ml total volume with preservative-free 0.9% normal saline”. The clinical trial studied Depodur made up to a 5ml total volume by dilution with preservative-free 0.9% normal saline in the hospital pharmacy. This is satisfactory.

II.1.7 Metabolism/Elimination

The metabolism and elimination of morphine sulfate administered systemically or epidurally in aqueous solution are reasonably well established and the literature submitted by the company provides sufficient documentation. The clearance of Depodur was as expected for morphine sulfate. Clearance was reduced by 13% in the over 65s compared with under 65s. This is unlikely to be clinically relevant as the product does not work systemically and plasma levels are largely sub-therapeutic.

II.1.8 Special populations

No PK differences were apparent between healthy volunteers in Phase I and patients undergoing operations.

No data are presented in patients with renal or hepatic impairment. This is accepted for the reasons given above. Adverse effects associated with morphine in renal impairment (e.g. respiratory depression) are attributable to the accumulation of morphine-6-glucuronide, a renally excreted active metabolite. As confirmed by bibliographic references submitted in the dossier, clinically significant problems would not be anticipated following a single epidural dose of Depodur. There are no new issues relating to renal impairment that might be applicable to the new formulation, that are not already well characterised in the literature.

II.2 Pharmacodynamics

The pharmacodynamics of morphine sulfate administered both systemically and epidurally is well characterised in the literature. Section 5.1 of the proposed SPC for Depodur provides the following information:

Morphine acts as an agonist at opiate receptors in the CNS, particularly mu and, to a lesser extent, kappa receptors. Mu receptors are thought to mediate supraspinal analgesia, respiratory depression, and euphoria, and kappa receptors, spinal analgesia, miosis, and sedation. Morphine also has a direct action on the bowel wall nerve plexuses, causing constipation.

Epidural administration of morphine sulfate results in analgesia without attendant loss of motor, sensory, or sympathetic function. As compared to systemic administration or morphine at comparable doses, epidurally administered morphine results in improved analgesia with increased duration.
Depodur is a sustained-release formulation of the active ingredient morphine sulfate designed for epidural administration. Morphine released from Depodur is absorbed both neuraxially and systemically.

Page 7 of the clinical overview provides a summary of the pharmacodynamic activity of morphine sulfate.

**Interactions with drugs used in regional or general anaesthesia**

Morphine sulfate has been administered epidurally in anaesthetic practice for many years. There are a number of known systemic pharmacodynamic interactions with other drugs used in anaesthesia including CNS depressants, general anaesthetics, neuroleptics, and alcohol. These systemic interactions are likely to be no greater than for non-encapsulated morphine due to the lower Cmax for Depodur. *Other pharmacodynamic interactions might be expected at a spinal level e.g. clonidine. These should be considered by the company and mentioned as appropriate in section 4.5 of the SPC.*
III CLINICAL EFFICACY

III.1 Introduction and overview

A substantial bibliographic dossier and compressive review of it is presented. It meets the regulatory requirements for bibliographic applications such as provision of tabulated study synopses. However a number of the cited references are not included in the dossier but are available on request. They should be submitted unless otherwise justified. In particular those references relevant to safety and efficacy issues raised by CSM should be provided.

Efficacy information from the bibliographic dossier

The efficacy of intravenous and epidural morphine for post-operative analgesia is fully and unequivocally established and is fully demonstrated by the bibliographic dossier. It requires no further detailed assessment.

Efficacy information from the clinical development programme

The Depodur clinical development programme in post-operative pain management consisted of two Phase II studies (C0401-008 and C0401-009) and four Phase III studies (SKY0401-011, SKY0401-012B, SKY0401-015, SKY0401-017). SKY0401-011 and SKY0401-012B are considered pivotal. Their key features are summarised below:

Phase II

008 Open label dose finding study (hip arthroplasty, 51 subjects).
009 Randomised double blind placebo controlled Phase II dose finding study (hip arthroplasty, 200 subjects).

Phase III

011 Pivotal placebo controlled trial (hip arthroplasty, 200 subjects).
012B Pivotal active comparator controlled trial vs. unencapsulated epidural morphine (lower abdominal surgery, 506 subjects).
015 Randomised double blind dose finding active comparator study vs. unencapsulated epidural morphine (elective caesarean section, 200 subjects).
017 Active comparator controlled trial vs. PCA morphine and using pain score as primary endpoint (lower abdominal surgery, 506 subjects).

Patient populations
Both somatic and visceral postoperative pain models (major orthopaedic and abdominal
surgery) were studied in the pivotal efficacy studies. This is in line with the CPMP draft
guideline on the investigation of treatments for nociceptive pain and is satisfactory to
justify a general indication of “the relief of post-operative pain”.

Patients were all ASA I to III. Spinal or General Anaesthesia was employed but epidural
anaesthesia was an exclusion criterion in all studies (discussed further below). Other
inclusion and exclusion criteria in the Phase III studies were satisfactory.

Efficacy endpoints

- The choice of primary efficacy endpoint in the phase III placebo-controlled studies
has been the subject of considerable debate involving the FDA, CPMP and national
European regulators. The company has argued that the amount of PCA-delivered IV
fentanyl used post-operatively is an appropriate primary efficacy endpoint. This
endpoint has been used to assess the efficacy of post-operative analgesia in studies
reported in the literature (references supplied) and in the Phase II trials it appeared
to show adequate sensitivity. Due to the availability of rescue Patient Controlled
Analgesia (PCA) to all patients at all time points, the company argued that the use
of pain scores as an endpoint would not be useful, whilst quantification of the
amount of PCA rescue medication should effectively differentiate between the
treatment groups. This seems generally reasonable.

In the formal scientific advice the CPMP pointed out that in a placebo controlled trial, a
pain intensity difference should be expected during the first hours after surgery, as was
seen in the SKY0401-009 study (where the same levels of analgesia were obtained only
after 18 hours). Therefore the company was advised to consider pain measurement scales
as a co-primary variable in such a study. In addition the company was advised that with
respect to the duration of efficacy the “time to first fentanyl use” would be more
informative than the amount of post-operative fentanyl usage through 48 hours post-dose in
demonstrating superiority of Depodur over regular morphine.

The company has chosen to retain 48 hour post-operative fentanyl usage as the primary
efficacy endpoint for the pivotal placebo controlled efficacy study SKY0401-011. Key
secondary endpoints included pain measurement scales and time to first fentanyl use,
thereby at least partly addressing the CPMP’s advice. The company provides the following
argument:

*The time to first fentanyl use is an efficacy variable that is not representative of the
entire analgesic effect of pre-emptive morphine given pre-operatively via the epidural
route, as in the Phase III trials. This is because rescue medication is often required
much earlier than would be expected from the duration of action of epidural morphine.
This is exemplified by the median time to the use of rescue medication following 5 mg of
unencapsulated morphine epidurally in Study SKY0401-012B. This was 3.6 hours after
its pre-operative administration, which is far less than the duration of action of 5-6 mg
of unencapsulated epidural morphine of 12-18 hours. This shows that the time to
the first rescue medication only considers the initial efficacy of epidural morphine and*
not its efficacy throughout its duration of action. For this reason, time to rescue medication is not an appropriate primary efficacy variable in this case, despite being generally recommended as such in studies of pre-emptive analgesia by the CPMP guideline.

ASSESSOR’S COMMENT
The argument on choice of primary endpoint is fully accepted. Although time to first fentanyl use would provide information on the duration of complete analgesia it would provide no information on the degree of analgesia provided beyond this time. As the purpose of this modified release product is to provide analgesia through the second post-operative day it is appropriate to choose a primary endpoint that would provide this information. Similarly pain measurement scales would be relevant during the first hours after surgery (it is important to show the time to onset of “full” analgesia with the modified release product), but not into the second post-operative day. This assessment report will present the results for both the company’s chosen primary efficacy endpoint and for the CPMP’s proposed co-primary endpoints. If all of these endpoints give positive results this would allay any possible concerns over which of them to specify as primary.

In response to advice from the FDA the company chose an unusual primary efficacy endpoint for the pivotal dose ranging efficacy study 12B. This was confirmation of linear dose-response based on the slope of the curve of total 48 hour fentanyl use against dose. More conventional analyses were chosen as secondary endpoints.

Some amendments to the SPC will be necessary in order adequately to reflect the inclusion and exclusion criteria in the Phase III studies, for example contraindication of concurrent epidural anaesthesia.

III.2 Phase II dose ranging studies

The Phase I study 003 concluded that 30 mg was the maximum tolerated dose of Depodur in healthy volunteers, and that doses of 20 to 30 mg may be safe and effective in pain management and should be further studied in surgical pain models. In the subsequent two Phase II dose ranging studies, 008 and 009 patients were permitted to self-administer supplemental IV fentanyl and the primary efficacy measure was the assessment of fentanyl usage for 24 and 48 hours following study drug administration.

Study 008
This was an open label dose finding study, comparing 10, 15, 20, 25 and 30mg of Depodur with 5mg of regular epidural morphine in a total of 51 subjects undergoing hip arthroplasty under regional (spinal) anaesthesia.

Patients given Depodur demonstrated a dose-related reduction of fentanyl requirements compared to patients given unencapsulated morphine 5mg.
Median time to first fentanyl use was 5.9 h for unencapsulated morphine 5mg, 17.5h, 36.4h and 35h for 10mg, 20mg and 30mg Depodur, respectively. This suggests that 20mg is the appropriate dose in this patient population with somatic pain, as it is markedly superior to 10mg and just as effective as 30mg.

**Study 009**

This was the major Phase II dose finding study. It was a randomised double blind placebo controlled trial comparing 15, 20 and 25mg of Depodur with matching placebo in a total of 200 subjects undergoing hip arthroplasty under general anaesthesia. Patients receiving Depodur demonstrated a dose-related reduction of fentanyl requirements compared to placebo. Median time to first fentanyl use was 3.3 h for placebo, and 12.2, 24.8 and 16.1 h for 10 mg, 20 mg and 30 mg Depodur, respectively. Again this supports the choice of 20mg as the appropriate dose for further study.

**III.3 Pivotal efficacy study SKY0401-011**

**A Phase III, Randomised, Double-Blind, Placebo-Controlled, Parallel Group, Dose-Ranging Study to Evaluate the Safety and Efficacy of a Single Epidural Dose of Depodur in the Management of Post-Operative Pain in Patients Undergoing Hip Arthroplasty**

200 patients undergoing hip arthroplasty in the USA (25 centres) were randomised to receive a single epidural dose of Depodur 15mg, 20mg or 25mg, or saline placebo. All study medication was in a 5ml volume. The primary efficacy endpoint was total fentanyl use post-operatively as rescue medication.

The trial was initiated in January 2001 under the original protocol, which did not mandate a flush or wait time after test dose administration prior to study drug administration. 77 patients were enrolled under this protocol. Subsequently the protocol was amended, making the test dose optional but if administered it required a flush and 15 minute wait. 123 patients were enrolled under this amendment.

6 patients were excluded from the ITT efficacy analysis. 1 did not have the surgery and the other 5 were not followed for rescue medication use.

The results for the primary and secondary efficacy endpoints (ITT) are presented in the table:
The company concludes that, due to an increased incidence of AEs in the 25mg group, the recommended dose should be 20mg in adults <65 years. In patients >65 years maximal efficacy was achieved by 15mg so the lower dose is recommended in this age group.

**Statistical assessor’s comment**

**Patient accountability**

Trial 011 tested the efficacy of SKY0401 in the management of post-operative pain after hip arthroplasty. The trial compared placebo with 3 different doses of SKY0401 (15, 20 and 25mg).

A total of 200 patients were randomised into the trial. There were only 6 patients excluded from the ITT population, none of whom had received treatment.

**Randomised patients and reason for exclusion from ITT population by treatment group –**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo n = 49</th>
<th>SKY0401 15 mg n = 50</th>
<th>SKY0401 20 mg n = 49</th>
<th>SKY0401 25 mg n = 46</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Analyses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Fentanyl Usage Through 48 Hours (µg) Mean (SD)</td>
<td>2091 (1803)</td>
<td>663 (715)</td>
<td>485 (715)</td>
<td>371 (675)</td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Secondary Analyses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Fentanyl Usage Through 24 Hours (µg) Mean (SD)</td>
<td>1282 (985)</td>
<td>295 (342)</td>
<td>210 (288)</td>
<td>201 (325)</td>
</tr>
<tr>
<td>Total Fentanyl Usage &gt; 24 to 48 Hours (µg) Mean (SD)</td>
<td>788 (946)</td>
<td>368 (450)</td>
<td>275 (515)</td>
<td>167 (378)</td>
</tr>
<tr>
<td>Time to First Post-Operative Use of Fentanyl (Hours) Median</td>
<td>3.6</td>
<td>15.4</td>
<td>22.7</td>
<td>22.8</td>
</tr>
<tr>
<td>Number of Patients Receiving No Fentanyl Post-Operatively through 48 Hours (%)</td>
<td>1 (2%)</td>
<td>8 (16%)</td>
<td>14 (29%)</td>
<td>14 (30%)</td>
</tr>
<tr>
<td>Number of Patients Receiving No Fentanyl Post-Operatively through 24 Hours (%)</td>
<td>1 (2%)</td>
<td>20 (40%)</td>
<td>24 (49%)</td>
<td>22 (47%)</td>
</tr>
<tr>
<td>Number of Patients Receiving No Fentanyl Post-Operatively &gt;24 to 48 Hours (%)</td>
<td>3 (6%)</td>
<td>9 (18%)</td>
<td>18 (37%)</td>
<td>20 (43%)</td>
</tr>
<tr>
<td>Pain Intensity Evaluation at Rest (VAS AUC 0-48 Hours) Mean (SD)</td>
<td>1462 (745)</td>
<td>946 (767)</td>
<td>737 (663)</td>
<td>653 (714)</td>
</tr>
<tr>
<td>Number of Patients Rating Pain Control Good and Very Good at 24 Hours (%)</td>
<td>32 (65%)</td>
<td>43 (86%)</td>
<td>45 (92%)</td>
<td>42 (91%)</td>
</tr>
<tr>
<td>Number of Patients Rating Pain Control Good and Very Good at 48 Hours (%)</td>
<td>33 (67%)</td>
<td>41 (82%)</td>
<td>37 (75%)</td>
<td>42 (91%)</td>
</tr>
</tbody>
</table>
A similar adaptive randomisation scheme to that employed in trial 012B was used here, to achieve a balanced number of patients across treatment groups with respect to anaesthesia type (general or regional) and study site.

**Multiplicity**
As in trial 012B the applicant employed a closed testing procedure to account for multiple treatment groups. Only if an overall test for differences between treatment groups was significant were tests comparing the individual SKY0401 doses against placebo conducted. This is appropriate.

**Choice of primary endpoint**
As in trial 012B, the primary efficacy endpoint was the total IV fentanyl used for 48 hours post dose. This is an appropriate primary endpoint. The analysis of the endpoint (ANOVA on rank-transformed data) was also the same as in 012B.

**Missing data**
As only 5 patients did not provide complete data, this is not a critical issue.

**Opioid usage collected through 48 hours?**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>15mg</th>
<th>20mg</th>
<th>25mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>48</td>
<td>50</td>
<td>46</td>
<td>45</td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

**Results**
As in trial 012B the skewed nature of the data results in the mean not being a useful summary statistic. Attention should be placed upon the median in the tables below.

**Total IV Fentanyl use (µg) through 48 hours post dose**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>15mg</th>
<th>20mg</th>
<th>25mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>85</td>
<td>84</td>
<td>79</td>
<td>83</td>
</tr>
<tr>
<td>Mean</td>
<td>2091.4</td>
<td>663.0</td>
<td>485.4</td>
<td>370.6</td>
</tr>
<tr>
<td>Median</td>
<td>1605</td>
<td>400</td>
<td>250</td>
<td>250</td>
</tr>
<tr>
<td>p-value vs. placebo</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Overall p-value for difference between groups: p<0.0001

All active doses were highly significantly superior to placebo.

**Total IV Fentanyl use (µg) through 0-24 hours post dose**

MHRA PAR -Depodur Suspension for Injection PL20334/0002-4 - 40 -
Looking at the data split by 24 hour period again reveals that the majority of fentanyl use was in the first 24 hours. The 15mg group required more in the second period but the amount dropped in all other groups.

In the period 24-48 hours all doses of SKY0401 were vastly superior to placebo, demonstrating the sustained efficacy of the preparation. A strong dose response was seen over this period also, with higher doses providing efficacy. Analysis looking at only the last 4 hours provides further reassurance regarding long-term efficacy.

The absence of an active comparator means that this study cannot provide reassurance that patients are not placed at a disadvantage in the period immediately following surgery by using the long acting formulation rather than immediate release, although it is clear that SKY0401 is vastly superior to placebo over the first 24 hours.

Secondary analysis of pain score data also favoured SKY0401, showing that the decreased use of rescue medication was not at the cost of increased pain.

**Medical assessor’s additional comments**

- It is interesting that patients assessed the overall quality of analgesia at 24 and 48 hours as superior in all of the active groups, despite all having free access to rescue medication. This may be because patients tend to wait until the pain becomes troublesome before pressing the PCA button, rather than being more pre-emptive.
Blinding of the study does not appear to have been as robust as it might have been. The study report states that the administering anaesthetist was unblinded to study medication but was not involved in patient care, clinical assessments or data collection. Depodur and saline are visually indistinguishable so that other staff should remain blind but there is potential for unblinding if they have any communication with the unblinded anaesthetist. The company should provide further details on the unblinded administering anaesthetist in the Phase III studies including whether treatment allocation might have been known to the investigator prior to recruiting each patient. Also whether the unblinded anaesthetist knew the dose of Depodur administered or just whether the patient was given active or placebo. The latter scenario would be reassuring given the clear dose-response seen in the main studies.

Highly statistically and clinically significant superiority over placebo is shown for all three strengths of Depodur. This superiority was maintained throughout the second 24 hour period and a clear dose-response relationship is seen. 20mg clearly seems to be superior to 15mg whilst 25mg is superior to 20mg on some endpoints (including the primary endpoint) but not others (e.g. time to first post-operative use of fentanyl).

Notwithstanding the blinding issues, it may safely be concluded that epidural Depodur is superior to placebo. It will however be necessary to show efficacy relative to an Immediate Release morphine preparation.
III.4  Pivotal efficacy study SKY0401-012B

A Phase III, Randomised, Double-Blind, Dose-Controlled, Parallel Group, Dose-Ranging Study to Evaluate a Single Epidural Dose of Depodur in the Management of Post-Operative Pain in Patients Undergoing Lower Abdominal Surgery

Patient accountability

Trial 012B tested the efficacy of SKY0401 in the management of post-operative pain after lower abdominal surgery. The initial protocol was for a 5-arm trial comparing a placebo group and 4 doses of SKY0401 (10, 15, 20 and 25mg). Between February and July 2001, 40 patients were enrolled. Following discussions with European Regulatory authorities the protocol was changed from a placebo-controlled design to a “dose-controlled” design where a dose of the rest product which is expected to be sub-therapeutic is included in the trial instead of placebo. To this end a protocol amendment removed the placebo arm from the trial and added a SKY0401 5mg arm. In addition an active comparator was included, 5mg unencapsulated morphine sulphate (MS).

The decision was made that only patients randomised after the protocol amendment would be included in the ITT population. This is appropriate as the protocol change may have caused a change in patient expectations. It was also planned to exclude patients who did not undergo surgery.

There were an additional 11 patients excluded who did undergo surgery but then withdrew consent before receiving treatment. This is acceptable as the removal of untreated patients is not concerning in a double-blind trial.

Randomised patients and reason for exclusion from ITT population by treatment group – trial 012B

<table>
<thead>
<tr>
<th>Placebo</th>
<th>MS</th>
<th>5mg</th>
<th>10mg</th>
<th>15mg</th>
<th>20mg</th>
<th>25mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised</td>
<td>5</td>
<td>89</td>
<td>91</td>
<td>88</td>
<td>92</td>
<td>91</td>
</tr>
<tr>
<td>ITT</td>
<td>0</td>
<td>85</td>
<td>86</td>
<td>70</td>
<td>84</td>
<td>79</td>
</tr>
<tr>
<td>Reason:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amendment</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>17</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>No surgery</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Consent</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

Patients were randomised using “number adaptive randomisation”, to achieve a balanced number of patients across treatment groups with respect to anaesthesia type (general or regional) and study site. The probability of assignment was modified across the 6 treatment groups as a function of departure from the 1:1:1:1:1:1 ratio. The use of such a “minimisation” procedure seems reasonable with a large number of treatment groups. It is unfortunate that the procedure wasn’t re-set at the time of the protocol amendment, as it has lead to an imbalance between treatment groups, with the 10mg group having fewer ITT patients, as it had more patients enrolled in the original protocol.
**Multiplicity**

Because there were many treatment groups there was potential for multiple testing problems in the analysis of the trial if pairwise comparisons between treatment groups were performed. To account for this the applicant employed a closed testing procedure.

The primary analysis compared the combined SKY0401 10 15, 20 and 25mg groups against the SKY0401 5mg group. Only if this result was significant were tests comparing the individual higher SKY0401 doses against 5mg conducted. In addition the higher SKY0401 doses were compared against MS 5mg, although this was not considered part of the primary efficacy evaluation.

This closed testing procedure is appropriate and maintains the overall type I error at 5%. At the request of the FDA an initial step was added to the procedure, a linear regression analysis to test for a dose related decrease across the SKY0401 groups.

**Choice of primary endpoint**

The primary efficacy endpoint was the total IV fentanyl used for 48 hours post dose. This is an appropriate primary endpoint, and is much better than many alternatives sometimes proposed in this area.

Analysis of pain scores would not be expected to be particularly useful in a trial where rescue medication is allowed, as if the rescue is used appropriately all patients should be equally well controlled for the majority of the trial.

Time to first rescue medication would not be useful for this product because the aim is to sustain the level of relief that is gained from immediate release morphine into the longer term. As such it would not be expected to delay the time of first administration of rescue compared to morphine, but rather to sustain a low level of rescue usage over a longer period.

**Primary analysis assumptions**

The total fentanyl use was to be compared across treatment groups using analysis of variance (ANOVA), with terms for treatment and type of anaesthesia (general or regional). If the assumptions for the use of ANOVA were not met, rank-transformation of the data would be applied and ANOVA performed on the rank-transformed data instead. It is appropriate to use type of anaesthesia as a covariate as it was used as a stratification factor in the randomisation. Technically centre might also have been included for the same reason, but with a large number of centres the applicant was probably correct not to do so.

The data were highly skewed and the assumption that the data were normally distributed was not met. As such the analysis of IV fentanyl use was conducted on rank-transformed data. This is appropriate.
**Missing data**

If a patient prematurely withdrew from the study, the total fentanyl use over 48 hours would be projected. A per hour average use would be calculated based upon the 6 hours preceding withdrawal. This value would be multiplied by the number of hours remaining in the 48-hour period, and added to the amount of fentanyl actually used.

As the use of fentanyl tends to decrease over the 48 hour period this would result in poor values being imputed for missing patients, which seems appropriate. Analyses without imputation were also produced to help assess the robustness to missing values. As only 5 patients did not provide complete data, this is not a critical issue.

**Fentanyl usage collected through 48 hours?**

<table>
<thead>
<tr>
<th></th>
<th>MS</th>
<th>5mg</th>
<th>10mg</th>
<th>15mg</th>
<th>20mg</th>
<th>25mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>84</td>
<td>86</td>
<td>68</td>
<td>84</td>
<td>77</td>
<td>83</td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

**Results**

The data for fentanyl use through 48 hours did not follow the normal distribution. This is clear from the data presentations below, where the mean is much higher than the median, revealing a highly skewed distribution with the mean being pulled out by a few high values in each treatment group.

As planned in the statistical analysis plan, because of the lack of normality the ANOVA was performed using rank-transformed data. Another consequence of the lack of normality is that the mean is not a useful summary statistic and instead attention should be placed upon the median in the tables below.

**Total IV Fentanyl use (µg) through 48 hours post dose**

<table>
<thead>
<tr>
<th></th>
<th>MS</th>
<th>5mg</th>
<th>10mg</th>
<th>15mg</th>
<th>20mg</th>
<th>25mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>85</td>
<td>86</td>
<td>70</td>
<td>84</td>
<td>79</td>
<td>83</td>
</tr>
<tr>
<td>Mean</td>
<td>1217.7</td>
<td>1213.3</td>
<td>995.1</td>
<td>959.0</td>
<td>972.0</td>
<td>682.5</td>
</tr>
<tr>
<td>Median</td>
<td>1005</td>
<td>955</td>
<td>645</td>
<td>760</td>
<td>590</td>
<td>500</td>
</tr>
<tr>
<td>p-value vs. 5mg</td>
<td>0.045</td>
<td>0.126</td>
<td>0.022</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-value vs. MS</td>
<td>0.568</td>
<td>0.009</td>
<td>0.033</td>
<td>0.004</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

*Overall p-value for difference between SKY0401 groups: p=0.0015
p-value for linear dose response across SKY0401 groups (FDA primary analysis): p=0.0002*

The overall test was significant, revealing that there are differences between the SKY0401 groups. The test for a linear dose response was also significant, and suggested a significant trend for decreasing fentanyl use with increasing dose.

**Total IV Fentanyl use (µg) through 0-24 hours post dose**

<table>
<thead>
<tr>
<th></th>
<th>MS</th>
<th>5mg</th>
<th>10mg</th>
<th>15mg</th>
<th>20mg</th>
<th>25mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>85</td>
<td>86</td>
<td>70</td>
<td>84</td>
<td>79</td>
<td>83</td>
</tr>
<tr>
<td>Mean</td>
<td>677.3</td>
<td>662.4</td>
<td>559.1</td>
<td>592.1</td>
<td>598.9</td>
<td>404.0</td>
</tr>
<tr>
<td>Median</td>
<td>506</td>
<td>540.5</td>
<td>365</td>
<td>475</td>
<td>470</td>
<td>315</td>
</tr>
</tbody>
</table>
### Statistical assessor’s comments

Looking at the data split by 24 hour period reveals that the majority of fentanyl use was in the first 24 hours, with patients in all treatment groups requiring more medication over this period. This is as expected, because the level of pain would be expected to be greater in the hours just following the operation than 24 hours later.

The effect of treatment was small in the first 24 hours, with only the 25mg dose showing any real additional efficacy over the 5mg dose. However the trends favoured the 10-25mg doses of SKY0401 over MS. This provides evidence that SKY0401, primarily designed to provide long lasting efficacy, is still effective in the early period, and that patients are not placed at a disadvantage in the period immediately following surgery by using the long acting formulation.

The effect of treatment was more substantial in the second 24 hours, even though the fentanyl usage was lower across all groups. This is what would be expected, as SKY0401 is a sustained release formulation, as opposed to the immediate release MS. The large differences in fentanyl use in this second 24 hour period demonstrate that the objective of longer lasting efficacy has been achieved.

Secondary analysis of pain score data also favoured SKY0401, showing that the decreased use of rescue medication was not at the cost of increased pain.

### Medical assessor’s comments

Clearly this study is not comparing like with like as the proposed dose of Depodur (20mg) is four times higher than the normal epidural dose. Nevertheless the choice of 5mg unencapsulated morphine as the active comparator is appropriate. 5mg has been shown to be an appropriate dose for epidural administration, giving typically 16 to 24 hours of good quality analgesia, whilst higher doses are associated with an increased incidence of adverse events. The point of this study is to demonstrate that a single epidural dose of Depodur produces superior analgesic efficacy than can be achieved with a single epidural dose of unencapsulated morphine. In this context “superior” means good quality analgesia of a longer duration than is otherwise possible with a single epidural injection.

It is reassuring that Depodur appears to be as effective as unencapsulated morphine 5mg in the early post-op period. Unencapsulated morphine is known to be effective for 16–24
hours and, as would therefore be expected, it is in the second 24 hours that the therapeutic doses of Depodur showed their greatest superiority. This is most clearly seen in the last of the tables above, total IV fentanyl use through >24-48 hours post dose. 20mg produced maximal efficacy, justifying the SPC posology.

III.6 Study SKY0401-015

A Randomised, Double-Blind, Active-Controlled, Dose-Ranging, Parallel Group Study to Evaluate a Single Epidural Dose of Depodur in the Management of Post-Operative Pain in Patients Undergoing Elective Caesarean Section

This Phase II study in patients undergoing elective caesarean section under spinal anaesthesia was conducted in 79 patients at sites in the US. A combined spinal epidural technique was used. The epidural injection was administered via a catheter after delivery and clamping of the umbilical cord.

There were four treatment arms, SKY0401 5mg, 10mg and 15mg, compared with 5mg unencapsulated morphine. The primary endpoint for the study was quantity of rescue medication.

The 10mg and 15mg doses of SKY0401 were clearly superior to 5mg unencapsulated morphine in the second post-op day (reduced rescue medication requirements over 0-48 hours and 24-48 hours) but not on the first day. This is in line with other studies.

The conclusions that can be drawn on dose-response are limited. 5mg SKY0401 was not an efficacious dose whilst 10mg and 15mg showed apparently similar efficacy. The study was not powered sufficiently to conclude that 15mg was not significantly superior to 10mg, and 20mg was not tested.

Presumably lower doses were chosen for this study because of an expectation that pain would be less severe than in the other studies and that mothers would not wish to be excessively sedated by morphine. The justification for the SPC recommendation of a 10mg dose for patients undergoing elective caesarean section is weak. It would be more appropriate to make a more general statement that for operations associated with less severe pain and/or where freedom from the usual side effects of morphine is a priority, doses of 10-15mg may suffice.
III.5 Efficacy study SKY0401-017

A Randomised, Double-Blind, Active-Controlled, Dose-Ranging, Parallel Group Study to Evaluate a Single Epidural Dose of Depodur in the Management of Post-Operative Pain in Patients Undergoing Knee Arthroplasty

The applicant states that this “was originally a Phase II study, but was subsequently changed to a Phase III study”. It was conducted in 168 patients at 20 US sites and four Australian sites. The primary endpoint for the study is recalled pain intensity.

Trial 017 had three treatment arms, SKY0401 20mg and 30mg, and IV patient controlled morphine.

The trial design is significantly flawed leaving the data almost completely uninterpretable. After surgery patients received either SKY0401 or a sham epidural (placebo).

At the first request for rescue pain medication patients in the SKY0401 arm received IV hydromorphine until “no pain” status was reached. Patients on the patient controlled morphine arm received IV morphine until “no pain” status was reached. This use of different medications in the randomised arms is not acceptable. The two groups should be treated identically, apart from the randomised intervention.

Following this the PC morphine patients were set up with a morphine pump which they could self administer to gain satisfactory pain relief. The SKY0401 patients were given a saline (placebo) pump.

If pain relief were still inadequate the dose of the pump was increased for morphine patients, while SKY0401 patients received hydromorphine injection. A double dummy design ensured that these interventions remained blinded.

However again the rescue medication was different for the two groups, hydromorphine injection for the SKY0401 patients and IV morphine for the morphine group. Because of the difference in available rescue medications the randomised arms are no longer comparable, and the data from this trial cannot be used as pivotal evidence of efficacy. The trial is as much a comparison of IV morphine against hydromorphine injection as it is of SKY0401 against placebo.
III.7 Clinical studies in special populations

Elderly

No studies were conducted specifically in the elderly population. Adequate numbers of elderly patients received SKY0401 in the clinical trial programme. There are data in over 200 patients over 65 years of age and more than 50 patients over 75 years of age. This exposure in the elderly is adequate to establish the risk-benefit and the most appropriate dose for this age group and complies with the CPMP guideline on the clinical investigation of medicinal products in the elderly. Over 100 patients in this age group received a dose of 15mg or higher.

There are important differences in efficacy and safety/tolerability compared with younger patients. Body weight is generally lower and the elderly are more susceptible to the effects of opioids. The SPC recommends a dose of 15mg in patients older than 65 years (20mg in younger patients).

III.8 Assessor’s overall conclusions on clinical efficacy

Overall statistical conclusion

Trials 012B and 011 both provide clear evidence of the efficacy of SKY0401, and evidence that the efficacy is seen out to 48 hours post dose.

Trial 012B, by including an active comparator, provides evidence that patients using the extended release SKY0401 do not pay a penalty by losing early efficacy.

A strong dose response was seen. The 5mg dose appeared to be sub-therapeutic, while efficacy increased with increasing dose across the 15-25mg range.

III.9 Overall medical conclusion on efficacy

Overall, satisfactory evidence of efficacy is seen. 5mg is the maximum dose of epidural morphine that might be acceptably safe (but see below, safety section) and therefore is an appropriate comparator although the comparison with SKY0401 10-30mg is not comparing like with like. The main purpose of these studies is to demonstrate that SKY0401 produces more prolonged analgesia than can be achieved with unencapsulated epidural morphine, without repeated doses or an infusion. This objective has been achieved, perhaps most clearly illustrated by the results for rescue medication requirements (total PCA fentanyl use) through the second day (24-48 hours post dose) in the pivotal study 12B. The difference seen was clinically as well as statistically significantly superior to the unencapsulated epidural morphine comparator. A clear dose-response was seen, justifying the selection of 20mg as the recommended dose in the age <65 population. In the elderly a dose of 15mg provided optimal efficacy, comparable to a 20mg dose in younger adults. The efficacy data were comparable in both the visceral and somatic pain models.
IV CLINICAL SAFETY

A substantial bibliographic dossier and a compressive review of the safety information from it are presented. They provide copious information on the safety of unencapsulated morphine given intravenously and epidurally for post-operative analgesia.

As noted above a number of the cited references are not included in the dossier but are available on request. All cited references should be submitted unless otherwise justified, as is required by the regulations relating to bibliographic applications. In particular those references relevant to safety and efficacy issues raised by CSM must be provided.

Since there are major safety issues surrounding this product the company’s summary of clinical safety and selected narrative summaries are also appended to this assessment report.

Safety information from the bibliographic dossier

The safety profile and efficacy of intravenous morphine for post-operative analgesia is fully and unequivocally established and requires no further assessment. For epidural use the safety issues can be divided into those relating to circulating plasma levels of morphine and those relating to local activity in the CNS.

Systemic toxicity produced by morphine (excessive sedation, respiratory depression, nausea and vomiting etc.) is well characterised in the literature and is related to plasma levels, reflecting absorption of morphine into the circulation. It is therefore anticipated that systemic toxicity of Depodur will reflect plasma concentrations. By extrapolation of data from the PK studies on Depodur 5mg (assuming dose-linearity) Depodur 20mg appears to produce comparable peak plasma levels to unencapsulated epidural morphine 5mg. Some further information is required to confirm the plasma concentration – time curve following the 20mg dose of Depodur. Further information is also required on a comparison of the plasma concentration profile with the same 20mg dose of unencapsulated morphine given intravenously or intramuscularly.

As this is a modified release formulation a longer duration of potentially sedating plasma levels might be expected in some circumstances. The SPC advice (sections 4.4 and 4.7) should fully reflect this. Although most patients will be under close observation in hospital for at least 48 hours after administration this cannot be assumed.

Otherwise the safety profile of Depodur relating to circulating plasma levels of morphine is anticipated to be similar to unencapsulated morphine given orally or intramuscularly. The SPC therefore generally reflects those of established morphine products. Some SPC amendments are required. Section 4.8 should be extended to include a more comprehensive documentation of undesirable effects known to be associated with morphine, not just those reported in the Depodur clinical trial programme. Examples include disorientation and confusion, mood changes, dry mouth, facial flushing, palpitations, biliary or ureteric spasm, histamine release and bronchospasm.
Section 4.9 advises an initial dose of 0.4 to 2 mg of naloxone in the event of overdose. This might be too high in some situations in which it is desirable not to reverse the analgesia. The literature indicates that, where appropriate (managed by an anaesthetist), a smaller dose of naloxone might adequately reverse unwanted effects including (non-delayed) respiratory depression without reversing the analgesia produced by epidural morphine.

Adverse events relating particularly to the epidural route are also well characterised in the literature and include pruritus and delayed respiratory depression. They may be incompletely reversible by naloxone. Pruritus is well described in the literature as being particularly characteristic of the epidural route for opioids. It is included as a common (greater than 10%) adverse event in the SPC.

Morphine sulfate is a relatively water soluble opioid, largely ionised at physiological pH. Compared with more lipid soluble agents such as diamorphine and fentanyl it is less rapidly taken up into tissues (including epidural fat and the substantia gelatinosa) and tends to persist in the CSF. Rostral flow of CSF can lead to opioid drugs injected into the lumbar region reaching the brainstem a day or so later, resulting in respiratory depression due to direct action on the respiratory centres in the medulla. The tendency for morphine to persist in the CSF makes it much more liable to cause delayed respiratory depression by this mechanism.

For this reasons most anaesthetists use one of the more lipid soluble agents (usually diamorphine or fentanyl in the UK) to provide epidural opioid analgesia, despite the disadvantage of a shorter duration of action compared with morphine. The literature also indicates that a substantial body of opinion, at least historically, has considered that systemic opioids should not be used in conjunction with epidural morphine. However there seems to be wide agreement that it is acceptably safe to administer systemic opioids to patients who have received epidural diamorphine or fentanyl. The consensus view in 2004 on the safety of systemic opioids in conjunction with epidural morphine however is not clear. Because Depodur is not given in repeat doses it would be essential for rescue medication with systemic opioids to be permissible as other agents such as NSAIDs cannot be relied upon to provide adequate analgesia in the post-operative setting.

For Depodur, in which morphine persists in the epidural space even longer than after a single injection of non-encapsulated morphine, there is even greater concern over the possibility of delayed respiratory depression. In some ways the sustained release of morphine from the Depodur formulation is analagous to an epidural morphine infusion. The potential risk of delayed respiratory depression will need to be considered in comparison with the documented risks for both “single shot” and infusions of non-encapsulated morphine. The latter will be particularly important.

However the literature review does provide little information on the safety of epidural morphine infusions, in particular with regard to delayed respiratory depression. *The company should conduct a full and comprehensive review of this specific issue, including all relevant papers whether favourable to the company’s position or not. Review articles considering the risk-benefit of epidural morphine infusions might also be of relevance although efforts should be made to demonstrate an evidence base.*
Clinical development programme safety database

The total safety database comprises 927 patients exposed to Depodur including 230 given dose of at least 25mg and 228 given 20mg. This is sufficient for the most part to provide satisfactory information on the safety profile of Depodur relative to unencapsulated morphine given epidurally.

Safety data were collected for up to 7 days post-operatively, providing what appears to be a robust impression of the overall safety and tolerability profile. Level of sedation was recorded on a 5 point scale up to 48 – 72 hours. Blood gases were routinely monitored post-operatively in a two studies. A neurological assessment questionnaire was completed at day 30 in order to detect any relatively late neurological sequelae.

The safety data from the Depodur clinical development programme in post-operative pain management are summarised and reviewed in a good quality integrated summary of safety as well as in the individual study reports. The pattern of the common AEs was as expected for the patient populations for both GA and spinal anaesthesia, and no new safety or tolerability issues for Depodur were identified here. Some changes to the undesirable effects section of the SPC are required to reflect fully the known side effects of morphine.

For adverse events relating particularly to the epidural route (including delayed respiratory depression and local neural toxicity) the potential for new or greater safety issues relative to unencapsulated epidural morphine is of particular concern. The summary of clinical safety has therefore focused especially on these AEs. The emphasis of this assessment report will be on the undesirable effects particularly relevant to the epidural route and to the modified release formulation, and on safety aspects relevant to justification of dose advice.

DOSE RELATIONSHIP TO COMMON AES

The proposed dose of 20mg of Depodur recommended in the SPC is three to four times the normal recommended dose of unencapsulated epidural morphine. This is to a large extent justified by the PK data showing that Depodur 20mg probably produces peak plasma levels comparable to 5mg of unencapsulated morphine via the same route. Some reassurances and clarifications are required on these PK data however.

In general the clinical safety and tolerability data were in line with the expectations from the PK data. Dose-response relationships were seen for nausea, pyrexia, vomiting, urinary retention dizziness, and terms relating to respiratory depression. The frequency of these increased at doses greater than 20mg although doses of 30mg were still reasonably well tolerated (study 017) in the context of the alternative of systemic morphine. In terms of tolerability the doses recommended in the SPC are satisfactory in both adults and the elderly.
Respiratory depression

Respiratory depression is the most important side effects of opioids for post-operative analgesia. It occurs commonly in the early post-operative period and is related to the nature of the surgery and the anaesthetic as well as to opioid analgesia. Older patients with cardiopulmonary disease are most at risk. The applicant has provided a review of all reported cases of respiratory depression including narrative summaries of those considered severe or serious. As would be expected in a population of this type having major surgery there were a number of such cases.

At least one respiratory depression AE was reported in 24.8% of patients given Depodur. Reported incidences were comparable to those in the placebo, systemic opioid or unencapsulated epidural morphine control groups.

There was a clear dose-response across the Depodur treated patient.

The incidence and severity of reported cases of respiratory depression in the initial post-operative period was probably in line with that expected in this population.

Potential for delayed respiratory depression

Delayed respiratory depression is potentially lethal. However the reported incidence following epidural morphine, even though much greater than for agents such as diamorphine and fentanyl, is quite low. The potential risk following Depodur therefore might not necessarily be revealed by data from the clinical trial programme in 927 patients. Statistical analysis of the frequency of AEs indicating respiratory depression is likely to be less useful than detailed consideration of individual case reports. Narrative summaries of all deaths and serious AEs are provided in the dossier. Those that could possibly have resulted from delayed respiratory depression are briefly summarised below.

Deaths

There was one death due to unexplained cardiorespiratory arrest 21 hours after Depodur 20mg in a patient whose operation was cancelled after a colonoscopy under GA failed to locate a tumour. He was apparently well in the hours prior to his death. Other causes such as MI or PE are possible but there was no post-mortem (Patient 12B-83-119).

Serious late respiratory depression AEs

A number of the narrative summaries of serious AEs are suggestive of delayed respiratory depression although factors other than Depodur cannot be excluded. In a number overdosing of the PCA might conceivably be a factor although this has been shown to be uncommon in studies of intravenous fentanyl PCA. Some narrative summaries do not provide enough information on timing for any judgement to be made. The company should provide full details of the narrative summaries presented in order that a full causality assessment can be made.
Use of opioid antagonists

The summary of safety states that 33% of all Depodur treated patients received an opioid antagonists (most commonly naloxone) for the treatment of respiratory depression, compared with 20% of patients given unencapsulated epidural morphine and no patients at all given in either the IV opioid or placebo control groups.

Safety of lidocaine/adrenaline test dose

46% of patients given Depodur received a test dose of whom a majority (58%) were given Depodur within 15 minutes (the SPC advises to wait for at least 10 minutes). The clinical safety summary has explored the AE profile according to test dose. Only respiratory depression showed a clear pattern. At least one respiratory depression AE was reported in 21.2% of patients given no test dose, compared with 33.6% in those given a test dose within 15 minutes and 22.7% in those given a test dose followed by a wait of at least 15 minutes. This clearly contradicts the SPC, which states that “however, no clinically meaningful effects on safety or efficacy were observed, despite the administration of such a test dose.” This sentence should be deleted.

Safety in patients given therapeutic doses of epidural local anaesthetic

The route of administration for local anaesthesia during the clinical trials was intrathecal, with the Depodur being administered epidurally. No clinical trial evaluated co-administration of local anaesthetics and Depodur epidurally, although it would be normal clinical practice to use the epidural route for both opioid and local anaesthetic. A Combined Spinal Epidural (CSE) approach is also common clinical practice.

In the co-administration of local anaesthetics and Depodur epidurally, it would be necessary to contraindicate this practice on the SPC.

The company has proposed a study in volunteers looking at the kinetics of co-administration epidurally. Such a study would probably be useful but this pharmacokinetic data alone would not be unlikely to provide sufficient reassurance to permit co-administration of epidural local anaesthetics.

Safety relating to inadvertent intrathecal injection

The SPC gives the following advice:

No clinical studies have evaluated the safety of administration of Depodur into the intrathecal space. Studies in dogs administered Depodur intrathecally demonstrated no toxicity attributable to the lipid component of Depodur. While the adverse effects observed in these dogs were typical opioid side effects consistent with the dose of morphine administered, profound and prolonged respiratory depression would be expected in humans.

Rare cases of inadvertent intrathecal injection inevitably happen from time to time despite precautions to avoid it. Profound and prolonged respiratory depression would be expected
following intrathecal injection of Depodur. The SPC advises that it “should be administered by or under the direction of a physician experienced in the technique of epidural administration and who is thoroughly familiar with the labelling of this product”. This should be made more robust to ensure that only those with expert resuscitation skills, normally an anaesthetist, should administer it. An orthopaedic surgeon might be experienced in the technique of epidural administration but not in dealing with an acutely apnoeic patient. Adequate resuscitation facilities must be available.

Safety relating to incorrect storage

Administration of Depodur that has been incorrectly stored could be potentially dangerous as the modified release mechanism may fail. Pharmaceutical data indicate that freezing results in 38% of the morphine content being available as free morphine (normally 1.5%). This could potentially result in an excessive dose of essentially Immediate Release morphine being delivered. The SPC gives the following advice:

4.2. Posology and method of administration
Protect Depodur from freezing. Do not administer Depodur if it is suspected that the vial has been frozen.

6.4. Special precautions for storage
Store at 2° to 8°C (in a refrigerator). Protect from freezing and avoid aggressive shaking.

Further SPC information on the implications of incorrect storage should be given in order to ensure that health professionals are fully aware of the dangers. The company should provide information on the likely plasma concentration – time curve following administration of a 20mg dose of Depodur that has been subjected to freezing. The company is asked to consider whether the packaging could include an indicator that might warn if the product had been exposed to potentially dangerous temperatures.

Safety relating to the lack of an in-line filter

The SPC advises “do not use an in-line filter during administration of Depodur”. This is acceptable as the product is presented in a rubber topped vial rather than an ampoule which might contain glass fragments.

Conclusions on safety

There are major safety concerns. The most important is the potential for delayed respiratory depression, as this is potentially lethal. Acceptable safety of unencapsulated epidural morphine has not been demonstrated by the bibliographic dossier. Indeed there is a considerable body of evidence that the greater risk of delayed respiratory depression compared with agents such as diamorphine and fentanyl makes it an unsuitable choice for epidural use. The validity of a bibliographic application rests on the product having “a well established medicinal use, with recognised efficacy and an acceptable level of safety.”
The company needs to provide further justification that this is the case via the epidural route.

A number of the narrative summaries of one death and a numerous serious AEs are suggestive of delayed respiratory depression although factors other than Depodur cannot be excluded. Some narrative summaries do not provide enough information on timing for any judgement to be made. The company should provide full details of the narrative summaries presented in order that full causality assessments can be made.

The company should provide further details of the use of opioid antagonists for the treatment of respiratory depression, for each dose level compared with control groups.

Co-administration of therapeutic doses of local anaesthetics and Depodur epidurally should be contraindicated. Notwithstanding this, further data on the potential interaction should be provided.

V. CLINICAL EXPERT REPORT

A satisfactory clinical overview is provided by an experienced anaesthetist.

VI. PRODUCT LITERATURE

VI.1 SPC

1. The SPC should be amended as per the recommendations of the UK advisory Committee.

VI.2 PIL

The PIL is generally satisfactory. The PIL should be amended in line with changes to the SPC.

VI.3 Labels

The labels are medically satisfactory. The presentation adequately distinguishes the product from other injectable morphine preparations.

VI.4 Comments on application form

The MAA forms are satisfactory.
VII. CONCLUSIONS

Clinical pharmacology

The pharmacodynamic activity of epidural morphine is well documented in the bibliographic dossier. The Depodur preparation does not appear to differ from unencapsulated morphine in this regard.

The pharmacokinetic profile of Depodur is reasonably well demonstrated and appears appropriate for the purpose of providing 48 hours of analgesia following a single administration. Peak plasma levels are probably comparable to those following epidural unencapsulated epidural morphine 5mg, although clarification of this information is required. Levels approaching Cmax are maintained on a plateau for 4 hours followed by a long decline over 24-48 hours. This PK profile is in line with the claims made for the product.

Efficacy

Satisfactory evidence of efficacy is seen in both the visceral and somatic pain models. The clinical studies have shown that Depodur produces significantly more prolonged analgesia than can be achieved with unencapsulated epidural morphine, without repeated doses or an infusion. A clear dose-response was seen, justifying the proposed posology.

Safety

The acute safety and tolerability profile is comparable to that of epidural unencapsulated morphine 5mg. These AEs are related to plasma levels and are largely predictable.

There are major concerns relating to the potential for delayed respiratory depression. The bibliography has not shown epidural unencapsulated morphine to have acceptable safety in this regard, especially in comparison with alternative lipid soluble agents such as diamorphine. The modified release nature of Depodur might increase the risk further. A number of serious adverse events reported in the clinical trials might have been due to delayed respiratory depression.

Local anaesthetics similarly disrupt the lipid vesicles causing release of free morphine and concurrent epidural anaesthesia should therefore be contraindicated, at least until further clinical data on this interaction are available. This is unfortunate, as it would have been useful to be able to inject both local anaesthetic (for surgical anaesthesia) and Depodur (for post-op anaesthesia) into the epidural space at the same time. A combined spinal/epidural (CSE) approach will be necessary to achieve a similar result. The company plans to conduct a clinical study into this interaction. These data should help to establish whether local anaesthetic may safely be injected via the epidural catheter at a later time, for example in the event of the spinal block wearing off.

The potential for overdosing due to failure of the modified release mechanism if the product is stored incorrectly (especially freezing) requires further consideration.

Risk-benefit

The risk-benefit is considered negative due to concerns over safety.
VIII. CLINICAL AND PRE-CLINICAL ASSESSORS' CONCLUSIONS

1. All cited references should be submitted unless otherwise justified, as is required by the regulations relating to bibliographic applications. In particular those references relevant to the issues raised by CSM must be provided.

2. There are major concerns relating to the potential for delayed respiratory depression. The bibliography has not shown epidural unencapsulated morphine to have acceptable safety in this regard, especially in comparison with alternative lipid soluble agents such as diamorphine. The modified release nature of DepoMorphine might increase the risk further. A number of serious adverse events and one death reported in the clinical trials might have been due to delayed respiratory depression. They include 12B-36-134, 12B-74-103, 12B-83-119, 17-08-461, 17-12-454, 17-23-416, and 17-53-401. The fullest possible details of these cases should be provided, especially regarding other administered opioid agents and the timing of events.

3. The company should provide further information to clarify the plasma concentration – time curve following the 20mg dose of Depodur. The PK studies were performed on Depodur 5mg and dose-linearity cannot be assumed. A comparison with the same 20mg dose of unencapsulated morphine given intravenously or intramuscularly should be provided.

4. The company should provide clarification of the unlinding of the anaesthetists in the main studies. The administering anaesthetist was apparently unblinded to study medication but was not involved in patient care, clinical assessments or data collection. Depodur and saline are visually indistinguishable so that other staff should remain blind but there is potential for unblinding if they have any communication with the unblinded anaesthetist. The company clarify whether treatment allocation might have been known to the investigator prior to recruiting each patient. Also whether the unblinded anaesthetist knew the dose of Depodur administered or just whether the patient was given active or placebo. The latter scenario would be reassuring given the clear dose-response seen in the main studies.

5. Administration of Depodur that has been incorrectly stored (especially frozen) could result in an excessive dose of essentially Immediate Release morphine being delivered to the patient due to failure of the modified release mechanism. In addition to SPC changes the company is asked to consider whether the packaging could include an indicator that might warn if the product had been exposed to potentially dangerous temperatures. The company should provide information on the likely plasma concentration – time curve following administration of a 20mg dose of Depodur that has been subjected to freezing.
COMMITTEE ON SAFETY OF MEDICINES RECOMMENDATION – 24 June 2004

The UK Advisory Committee considered the licence application on 24 June 2004 and reported that, on the evidence before them, the Committee could not recommend the granting of marketing authorisation on the grounds of quality, safety and efficacy.

The main objections related to:

1. Concerns about the safety profile with respect to delayed respiratory depression
2. Dose linearity of the pharmacokinetics
3. Possible failure of the modified release mechanism resulting from the syringe.

Additionally, a number of points relating to the Summary of Product Characteristics, PIL and packaging were raised.

ASSESSMENT OF APPLICANT’S RESPONSE

On the 10th September 2004 the applicant submitted further documentation in support of its application.

The clinical assessors’ comments relating to this additional documentation is presented below.

**General point**
All cited references should be submitted unless otherwise justified, as is required by the regulations relating to bibliographic applications. In particular those references relevant to the issues raised by the Committee on Safety of Medicines (CSM) must be provided.

**SkyePharma Response:**
Cited references not already included in Module 5 are provided in this response. In particular, a copy of the literature review from the original application is included along with copies of all cited references in Appendix 4. Additional references cited in clinical protocols or study reports (and not provided in the original application) are included in Appendix 5.

**Assessor’s comment**
This is a much more comprehensive bibliographic dossier than that provided in the original submission. All reference are provided in full. It is considered that it now complies with the regulations relating to bibliographic applications.

**Specific points**

1. There are major concerns relating to the potential for delayed respiratory depression. The bibliography has not shown epidural unencapsulated morphine to have acceptable safety in this regard, especially in comparison with alternative lipid soluble agents such as diamorphine. The modified release nature of Depodur might increase the risk further. A number of serious adverse events and one death reported in the clinical trials might have been
due to delayed respiratory depression. They include 12B-36-134, 12B-74-103, 12B-83-119, 17-08-461, 17-12-454, 17-23-416, and 17-53-401. The fullest possible details of these cases should be provided, especially regarding other administered opioid agents and the timing of events.

**SkyePharma Response**

SkyePharma has prepared a thorough literature review, internal data assessment, and risk-benefit analysis of the potential for morphine, SKY0401, and alternative lipid soluble agents to produce delayed respiratory depression when used for post-operative pain management. This document is provided in Appendix 6.

The CSM expressed concerns related to the potential delayed respiratory depression that resulted from the administration of SKY0401 in the following cases: 12B-36-134, 12B-74-103, 12B-83-119, 17-08-461, 17-12-454, 17-23-416 and 17-53-401. The detailed narratives and Case Report Forms (CRFs) are presented in Appendix 7.

It is important to note that all patients listed above received doses of SKY0401 that were **higher** than the doses of SKY0401 recommended for the commercial product. In the proposed SPC, the following dosing guidelines are in place: for patients younger than 65 years of age 20 mg and for patients at or older than 65 years of age 15 mg. In addition, in most cases (except patient 12B-83-119) patients received supplemental opioid medications. In the case of patient 12B-83-119, the absence of pain stimuli (i.e., cancelled surgery) could have been the contributing factor for possibly developing respiratory depression, even though the death of the patient could have been due to other cause(s).

**Assessor’s comment**

**Literature review**

The company has provided a relative risk assessment of the risk of delayed respiratory depression. There is no independent report. A review is provided of the literature relating to the potential for opioids including morphine and more lipid soluble agents to produce late respiratory depression. The review is generally well balanced and of good quality. The assessor has reviewed the papers cited in the report.

The report cites references from 1996-7 indicating that, whilst diamorphine and fentanyl are generally used in preference to morphine by the epidural route in the UK for safety reasons, this was not the case in much of the rest of Europe at that time. The references presented do not indicate whether this remains the case today. With the greater availability of infusion pumps today this may not be the case. This question is however raised of whether typical UK anaesthetic practice might be overly cautious regarding the use of epidural morphine.

There will always be an element of under-reporting of medical events such delayed respiratory depression, hence some low rates quoted by some sources, but there is reasonable agreement in the literature that this complication occurs in approximately 1% of patients receiving epidural morphine (figures of up to 3% are reported). Of these a proportion will be potentially life threatening events and a small number might result in death.
The company compares the 1% incidence of delayed respiratory depression to comparable figures quoted for acute respiratory depression following enteral or parenteral opioid administration (including PCA). There are however important differences. Acute respiratory depression results essentially from overdosing a patient with strong opioids and is quickly recognisable and treatable. If strong opioids are prescribed with care on an individualised basis the risks should be minimal and are outweighed by the benefits.

In contrast delayed respiratory depression occurs unpredictably, without excessive doses being administered, and often at a time when it might not be easily recognisable. There are numerous reports of patients having a respiratory arrest only a short time after being fully awake and alert. It is believed that this corresponds to the point at which morphine in the CSF reaches the brainstem by rostral flow. In practice the necessary observation and monitoring to detect delayed respiratory depression, for example during the night after an operation, would be full High Dependency monitoring. In such a setting epidural infusions are commonly employed unless there are contraindications (sepsis, bleeding diathesis), allowing for dose titration and as long a duration of analgesia as required.

It has been said that delayed respiratory depression does not occur in association with lipophilic agents (fentanyl, diamorphine) administered epidurally. There are however some case reports indicating that this might not be the case. Nevertheless it is clear from the literature that such cases are exceptionally uncommon in comparison with morphine, for which this complication is relatively common. Morphine does however have clear advantages in the duration of analgesia achieved.

It is not clear why catastrophic delayed respiratory depression occurs in a small minority of individuals whilst in most cases presumably no significant amounts of morphine reach the brainstem. Simple diffusion alone would be unlikely to result in significant drug reaching the brainstem from the lumbar area so perhaps individual differences in CSF bulk flow might be the explanation.

In the UK it was widely stated that the use of systemic opioids was contraindicated in patients who had received epidural opioids. Since the use of lipophilic opioids epidurally has taken over from morphine in the UK, consensus opinion appears to be that it is safe to supplement epidural analgesia with systemic opioids, provided that the opioid given epidurally is lipophilic. The literature presented in the dossier appears to give strong support to the view that it is NOT safe to supplement epidural morphine analgesia with systemic opioids except with full High Dependency monitoring. A high proportion of the cases of severe delayed respiratory depression reported in the literature are in association with systemic opioids, but not temporally related to their administration. In the case of Depodur this would be problematic because it is given as a single shot dose without the possibility for dose titration. It is inevitable that some patients will not achieve adequate analgesia. If systemic opioids are to be contraindicated then only non-opioid rescue medical would be permissible. This might result in inadequate analgesia for an extended period.

Review of safety data from the clinical trial programme

The company has provided a further review of the safety database from the clinical trial programme focusing on respiratory depression. Much of it relates to early respiratory depression which is common in post-surgical patients treated with any type of strong opioid and not directly
relevant to the question in hand. We are only interested here in the risk of potentially catastrophic delayed respiratory depression.

The company points out that a number of patients in whom respiratory depression was reported received doses of SKY0401 that were higher than the doses recommended in the proposed SPC (20mg, 15mg in the elderly). They have accordingly not included them in the review. This is not acceptable as these cases are highly relevant to the discussion. They include all seven patients specifically mentioned in the CSM’s point 1. Other than these the company states that there were 6 patients who met the criteria for delayed respiratory depression, giving a total of 13 (2% of patients).

The company has submitted the full documentation, including Case Report Forms (CRFs), for all cases of possible respiratory depression including the specific cases identified in the CSM’s letter. The narrative summaries for the cases of possible delayed respiratory depression, and the key aspects identified by the medical assessor from the full documentation, are appended to this assessment report for the CSM.

In these 13 cases respiratory depression, often of sudden and unpredictable onset and profound, was reported between 6 and 21 hours following SKY0401 administration. All cases required naloxone, nine were judged to be “serious”, at least four required emergency resuscitation, and one patient died following an unexpected cardio-respiratory arrest. A full review of the 13 cases indicates that in most there is no plausible alternative explanation for the episodes of respiratory depression. The amount of systemic fentanyl (a relatively short acting agent) administered in the post-operative period was in most cases insufficient to have caused the event on its own, or in other cases to have caused such a long duration of the respiratory depression. Systemic opioid (fentanyl plus systemically absorbed morphine) may have contributed to some events but in most if not all cases were clearly not the primary cause.

The death occurred in a 74 year old man who received 20mg of Depodur but whose operation was cancelled (see narrative summaries appended). He had a fatal unexpected cardio-respiratory arrest 21 hours later. Whilst there are other possible explanations (he did have a colonoscopy and a quick GA) delayed respiratory depression due to epidural Depodur appears by far the most likely. The fact that he was older than the 65 year cut off for the 20mg dose (the dose recommendation in elderly is 15mg) is not particularly reassuring.

Conclusions

The detailed review of the literature on the issue of delayed respiratory depression provided by the company in the response documentation has not shown acceptable safety for either epidural unencapsulted morphine or Depodur with respect to delayed respiratory depression. Alternative lipid soluble opioids such as fentanyl and diamorphine have been shown to produce a much lower risk of this potentially fatal complication and can provide a long duration of titratable analgesia when given by epidural infusion.

13 cases (2%) of probable delayed respiratory depression were reported in the clinical trials including a number of life threatening situations and one death more likely than not to be directly due to Depodur. This level of risk is not justified by the advantages of the product (e.g. no complications from an indwelling epidural catheter, no need for an infusion pump) compared with other options for achieving long lasting analgesia with strong opioids.
Based on the PK data there are grounds for thinking that 20mg of modified release Depodur might increase the risk further compared with the usual 3-6mg of unencapsulted morphine. The applicant has provided no data or argumentation to address this possibility.

In conclusion there remain major concerns about the high risk of serious events and fatalities resulting from delayed respiratory depression with epidural morphine, which are likely to be exacerbated by the proposed delayed release formulation.

**Point outstanding**

2. The company should provide further information to clarify the plasma concentration - time curve following the 20mg dose of Depodur. The PK studies were performed on Depodur 5 mg and dose-linearity cannot be assumed. A comparison with the known pharmacokinetic profile of the same 20 mg dose of unencapsulated morphine given intravenously or intramuscularly should be provided.

**SkyPharma Response**

The CSM has stated that the pharmacokinetic studies were performed only on the 5-mg formulation of SKY0401 and requested further pharmacokinetic information on the 20-mg dose.

Pharmacokinetic data from the SkyPharma clinical studies (including DTC 96-003, SKY0401-008, -009, -011, and -012B) involved doses of SKY0401 from 5 to 30 mg and are summarized in Section 2.7.2 in the MAA submission (Summary of Clinical Pharmacology Studies). Specifically, pharmacokinetic results from the individual studies that involved the 20-mg dose are presented in Tables 2.7.2.2, 2.7.2.5, 2.7.2.6, 2.7.2.7, and 2.7.2.9 in the MAA submission. The comparison and analyses of pharmacokinetic results across studies can be found in Section 2.7.2.3, with the pharmacokinetic parameters from the pooled analysis presented in Table 2.7.2.14 in the MAA submission and in Table 1 below.

**Table 1: Morphine Plasma Pharmacokinetic Parameters (Mean, SD) Follow Epidural Administration of SKY0401: Pooled Analysis (Table 2.7.2.14 in the M. submission)**

<table>
<thead>
<tr>
<th></th>
<th>SKY0401 5 mg (n=14)</th>
<th>SKY0401 10 mg (n=36)</th>
<th>SKY0401 15 mg (n=71)</th>
<th>SKY0401 20 mg (n=63)</th>
<th>SKY0401 25 mg (n=32)</th>
<th>SKY0401 30 mg (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>9.4 (5.7)</td>
<td>20.0 (9.5)</td>
<td>18.6 (10.4)</td>
<td>26.4 (18.6)</td>
<td>22.6 (15.4)</td>
<td>47.3 (28.9)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-1&lt;/sub&gt; (ng•hr/mL)</td>
<td>30.9 (11.8)</td>
<td>135.9 (116.7)</td>
<td>100.9 (43.6)</td>
<td>160.8 (76.3)</td>
<td>158.3 (55.7)</td>
<td>297.9 (134.8)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (ng•hr/mL)</td>
<td>141.0 (10.6)</td>
<td>124.9 (98.1)</td>
<td>131.6 (73.7)</td>
<td>185.9 (81.4)</td>
<td>207.3 (77.7)</td>
<td>341.5 (136.9)</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (hr)</td>
<td>4.2 (2.1)</td>
<td>16.2 (19.7)</td>
<td>20.0 (20.6)</td>
<td>23.9 (25.4)</td>
<td>32.9 (24.2)</td>
<td>25.6 (14.6)</td>
</tr>
<tr>
<td>CL/F (mL/min/kg)</td>
<td>28.9 (9.7)</td>
<td>23.3 (13.5)</td>
<td>31.1 (21.8)</td>
<td>27.7 (12.1)</td>
<td>27.4 (10.6)</td>
<td>22.4 (8.8)</td>
</tr>
<tr>
<td>Vz/F (L/kg)</td>
<td>9.9 (3.8)</td>
<td>24.2 (26.6)</td>
<td>38.2 (28.2)</td>
<td>46.3 (40.2)</td>
<td>62.0 (31.2)</td>
<td>42.9 (16.7)</td>
</tr>
</tbody>
</table>

Pharmacokinetic data and the resultant pharmacokinetic parameters were obtained from a total of 63 patients who received the 20-mg dose of SKY0401.
The CSM also required further information on the plasma concentration–time profile of 20 mg of SKY0401 compared with the same 20 mg dose of unencapsulated morphine given intravenously or intramuscularly. This comparison was not directly evaluated as part of the clinical programme for SKY0401.

The published literature (provided in Appendix 8) contains four studies with single-dose pharmacokinetic information on intramuscular (IM) morphine doses ranging from 0.1 mg/kg to 0.2 mg/kg (presented in Table 2 below).

### Table 2: Single-Dose Morphine Pharmacokinetic Data: Published Literature

<table>
<thead>
<tr>
<th>Study</th>
<th>Route</th>
<th>Product</th>
<th>Dose (mg)</th>
<th>N</th>
<th>Cmax (ng/mL)</th>
<th>AUC (ng·hr/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chauvin M (1982)</strong></td>
<td>IM</td>
<td>UEM</td>
<td>0.2 mg/kg</td>
<td>6</td>
<td>60.0 (6.2)</td>
<td>165.2 (74.8)**</td>
</tr>
<tr>
<td></td>
<td>ED</td>
<td>UEM</td>
<td>0.2 mg/kg</td>
<td>6</td>
<td>50.3 (20.2)</td>
<td>177.9 (39.9)**</td>
</tr>
<tr>
<td></td>
<td>IM</td>
<td>[1]</td>
<td></td>
<td>6</td>
<td>42.8</td>
<td>117.9</td>
</tr>
<tr>
<td></td>
<td>ED</td>
<td>[1]</td>
<td></td>
<td>6</td>
<td>35.9</td>
<td>127.0</td>
</tr>
<tr>
<td><strong>Gustafsson LL (1982)</strong></td>
<td>ED</td>
<td>UEM</td>
<td>0.05 mg/kg</td>
<td>5</td>
<td>19.4 (5.4)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>IM</td>
<td>UEM</td>
<td>0.1 mg/kg</td>
<td>5</td>
<td>25.1 (5.6)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>ED</td>
<td>[2]</td>
<td></td>
<td>5</td>
<td>47.3</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>IM</td>
<td>[3]</td>
<td></td>
<td>5</td>
<td>30.6</td>
<td>-</td>
</tr>
<tr>
<td><strong>Nordberg G (1985)</strong></td>
<td>IM</td>
<td>UEM</td>
<td>0.1 mg/kg</td>
<td>5</td>
<td>46.3 (3)*</td>
<td>112 (7)* [4]</td>
</tr>
<tr>
<td><strong>Stanski DR (1978)</strong></td>
<td>IM</td>
<td>UEM</td>
<td>0.1 mg/kg</td>
<td>5</td>
<td>56.0 (1.8)*</td>
<td>-</td>
</tr>
<tr>
<td><strong>Stuart-Harris R (1999)</strong></td>
<td>IV</td>
<td>UEM</td>
<td>0.05 mg/kg</td>
<td>6</td>
<td>80.7 (21.1)</td>
<td>82.7 (19.1) [6]</td>
</tr>
<tr>
<td></td>
<td>SC</td>
<td>UEM</td>
<td></td>
<td>6</td>
<td>74.7 (14.0)</td>
<td>92.1 (17.1) [6]</td>
</tr>
<tr>
<td><strong>Pooled PK Analysis [8]</strong></td>
<td>ED</td>
<td>SKY0401</td>
<td>0.1 mg/kg</td>
<td>32</td>
<td>18.23 (8.45)</td>
<td>131.91 (105.34)</td>
</tr>
<tr>
<td><strong>Pooled PK Analysis [8]</strong></td>
<td>ED</td>
<td>SKY0401</td>
<td>0.1 mg/kg</td>
<td>60</td>
<td>25.10 (1.8)*</td>
<td>186.77 (83.63)</td>
</tr>
</tbody>
</table>

* - Standard Error, ** - AUC0–12


[1] – approximate dose normalized to 10 mg/70 kg, actual dose = 0.2 mg/kg
[2] – approximate dose normalized to 10 mg from mean dose, actual dose = 0.05 mg/kg
[3] – approximate dose normalized to 10 mg from mean dose, actual dose = 0.1 mg/kg
[4] – converted from µg·min/mL reported to ng·hr/mL
[5] – normalized in publication to 10 mg/70 kg
[6] – converted from nmol/L to ng/mL
[7] – concentration at first sample time following bolus injection
[8] – from Clinical Pharmacology Summary

Converted to an actual mg dose, these doses range from approximately 8 to 14 mg. In two of these studies, Chauvin et al 1982 and Gustaffson et al 1982, serum morphine concentrations following administration of intramuscular and epidural (unencapsulated) morphine were compared. The results of these two studies suggest that with epidural administration of unencapsulated morphine, the mean C\text{max} values may be slightly higher or slightly lower than those observed following intramuscular morphine administration. Following normalization to a dose of 10 mg/70 kg, the results of Chauvin indicate mean C\text{max} results of approximately 42.8 ng/mL and 35.9 ng/mL for intramuscular and epidural injections, respectively. In comparison, the mean normalized C\text{max} results from the Gustaffson trial were 30.6 ng/mL and 47.3 ng/mL for intramuscular and epidural injections, respectively. Across all four studies reporting pharmacokinetic results following intramuscular morphine administration, the mean C\text{max} ranged from 30.6 ng/mL to 56.0 ng/mL (after normalization to a dose of 10 mg/70 kg). In
the study that administered a 10 mg intramuscular dose (Nordberg 1985) the mean $C_{\text{max}}$ value was 46.3 ng/mL. Since this trial is the largest of the reported studies ($N = 35$), the results from this study probably represent the most reliable point estimate.

Mean $C_{\text{max}}$ values were 18.2 ng/mL and 25.1 ng/mL following administration of SKY0401 at doses of 10 mg and 20 mg, respectively. The mean $C_{\text{max}}$ values at both dosage levels are substantially lower than those observed for 10 mg of intramuscular doses. Since the mean $C_{\text{max}}$ values following administration of a 20 mg SKY0401 dose are smaller than those observed following a 10 mg intramuscular morphine dose, it can be concluded that the peak systemic exposure would be substantially smaller relative to a 20 mg intramuscular morphine dose.

**Assessor’s comment**

These data are generally consistent with the expectation that the PK profile of SKY0401 (Depodur) is essentially dose-linear. The different mean values for Cmax and AUC for the different routes and strengths are not directly comparable due to confounding factors (different subjects etc) but the overall pattern is as expected. Cmax for unencapsulated morphine given either intramuscularly or epidurally is of the order of three to four times greater than that seen following the same dose of Depodur given epidurally. AUCs are broadly comparable. This is consistent with the profile expected for a depot product and shows the same pattern for the proposed therapeutic doses (normally 20mg) as seen for the 5mg dose. The plasma concentration – time curves data for Duramorph 5mg and Depodur 5mg (both epidurally) are shown graphically on page 6 of the original medical assessment report.

**Point cleared**

3. The company should provide the individual patient pharmacokinetic data from study SKY041-016.

**SkyePharma Response**

The SKY0401-016 study report is included in Module 5, Section 5.3.3.4.1 (volumes 9 – 12). The pharmacokinetic aspects of this study are covered in a separate report (within the overall study report) that begins in volume 11. Individual patient plasma concentration versus time data for morphine, morphine-3-glucuronide, and morphine-6-glucuronide are included in Appendix A of the report, Tables 1, 2, and 3, respectively. Appendix B of the report should have included individual plasma concentration versus time plots; however, those were inadvertently omitted from the document. A complete clinical pharmacokinetics report of study SKY0401-016, including tabulated and graphed individual patient concentration versus time data, is included in Appendix 9 of this response.
Assessor’s comment

SKY041-016 was the study that evaluated the effects of a test dose of lidocaine and adrenaline on the pharmacokinetic profile of a single epidural dose of Depodur. The data indicated that the mean plasma Cmax was increased by approximately 60% by a standard lidocaine and adrenaline test dose. The company was asked to provide the individual patient pharmacokinetic data in order to establish how great the effect of the test dose might be in individual cases and to establish whether there was any evidence of more major vesicle disruption in a minority of cases.

The raw data and graphical presentations in the company’s response do not include the AUC calculations at the different time points, as presented for the mean values. The best indicator of potential major dose dumping precipitated by a test dose is therefore the Cmax values. The range of Cmax values for each group, and the mean values, are presented in the following table.

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment Regimen Description</th>
<th>Mean Cmax</th>
<th>Highest Cmax</th>
<th>Lowest Cmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No test dose + SKY0401 15 mg + Flush</td>
<td>11.5</td>
<td>24</td>
<td>4.1</td>
</tr>
<tr>
<td>2</td>
<td>Test dose + Flush + 3 min wait + SKY0401 15 mg + Flush</td>
<td>30.2</td>
<td>40</td>
<td>15.9</td>
</tr>
<tr>
<td>3</td>
<td>Test dose + Flush + 10 min wait + SKY0401 15 mg + Flush</td>
<td>15.6</td>
<td>34</td>
<td>7.4</td>
</tr>
<tr>
<td>4</td>
<td>Test dose + Flush + 15 min wait + SKY0401 15 mg + Flush</td>
<td>11.4</td>
<td>20</td>
<td>2.0</td>
</tr>
<tr>
<td>5</td>
<td>Test dose + 3 min wait + SKY0401 15 mg + Flush</td>
<td>25.6</td>
<td>46</td>
<td>15.2</td>
</tr>
</tbody>
</table>

The individual plots show very considerable inter-individual variability even within each of the five groups. In some cases plasma levels decayed very rapidly while in other cases much slower release of morphine into the circulation was seen. This might be related to anatomical variations in the epidural space and the exact site of injection within it. The epidural space is a mixture of fatty, vascular and fibrous tissues that is far from homogeneous.

In the highest risk groups (2 and 5) the highest Cmax recorded was less than twice the mean, which in view of the high standard deviation is reassuring that no evidence of major dose dumping due to the test dose was seen in this study.

Nevertheless the individual patient data support the SPC advice that if a test dose is administered Depodur should not be administered for at least a further 10 minutes. The flush appears to make relatively little difference based on these data but appears to be a sensible measure. **Point cleared**
4. The company should provide clarification of the unblinding of the anaesthetists in the main studies. The administering anaesthetist was apparently unblinded to study medication but was not involved in patient care, clinical assessments or data collection. Depodur and saline are visually indistinguishable so that other staff should remain blind but there is potential for unblinding if they have any communication with the unblinded anaesthetist. The company should clarify whether treatment allocation might have been known to the investigator prior to recruiting each patient. Also whether the unblinded anaesthetist knew the dose of Depodur administered or only whether the patient was given active or placebo. The latter scenario would be reassuring given the clear dose-response seen in the main studies.

SkyePharma Response
As SKY0401 has a “milky” appearance that is visually distinguishable from saline placebo and unencapsulated morphine sulfate, an unblinded administering anaesthetist was employed in order to preserve the blind. Other than physically administering the study drug to the patients, these anaesthetists were uninvolved with patient care, clinical assessments, and data collection. Furthermore, the administering anaesthetists were instructed not to communicate with the blinded study staff.

Upon confirmation of the eligibility of a patient, the investigator would complete an Investigator Authorization for Randomization form. This form was given to the pharmacist, who then randomized the patient and obtained the treatment assignment via a telephone-based interactive voice response system (IVRS) or sealed envelopes (depending upon the study). The pharmacist subsequently prepared the study drug and placed it into a sealed opaque bag for transport to the operating room, at which time only the unblinded anaesthetist could open the bag and view the syringe. The pharmacist was the sole individual who had full knowledge of the exact treatment assignment (i.e., not only whether it was SKY0401 or placebo/active control, but the actual dose as well). The treatment assignment information was not disclosed to the unblinded administering anaesthetist.

Due to the randomization schemas and blocking that were employed in these trials, it was not possible for any staff member (whether it was the unblinded pharmacist or any other blinded staff) to have knowledge of treatment assignments prior to enrolling patients.

Assessor’s comment
This response is satisfactory and provides reassurances on some issues that were not entirely clear from the study reports. Blinding and randomisation procedures appear to have been as robust as reasonably possible.

Point cleared
5. Administration of Depodur that has been incorrectly stored (especially frozen) could result in an excessive dose of essentially Immediate Release morphine being delivered to the patient due to failure of the modified release mechanism. In addition to SPC changes the company is asked to consider whether the packaging could include an indicator that might warn if the product had been exposed to potentially dangerous temperatures. The company should provide information on the likely plasma concentration – time curve following administration of a 20 mg dose of Depodur that has been subjected to freezing.

SkyePharma Response

SKY0401 is sensitive to freezing, and the proposed labelling includes instructions such as “DO NOT FREEZE” and “Do not administer Depodur if it is suspected that the vial has been frozen.” To provide further assurance of product quality, SkyePharma proposes to include a freeze indicator in each carton of SKY0401. The initial part of this response discusses the freeze indicator. The second part of this response provides simulations of the plasma concentration – time curve following administration of a 20 mg dose of SKY0401 that has been subjected to freezing.

Freeze Indicator:

In the marketing application, SkyePharma had proposed packaging SKY0401 in cartons of individual vials. In the current plans, SKY0401 will be packaged in cartons of 5 vials. With the larger carton size, it will be possible to include a freeze indicator.

Therefore, SkyePharma plans to add a ColdMark™ 0ºC/32ºF Freeze Indicator to each 5-vial carton of SKY0401. The freeze indicator will be adhered to the inside of the carton lid, and will provide a visual, non-reversible record of temperature exposure below 0ºC/32ºF.

The ColdMark™ 0ºC/32ºF Freeze Indicator (Figure 1) is manufactured by:

Introtech, Inc.  
702 Birchwood Avenue  
P.O. Box 10505  
St. Paul, MN 55110  
Phone: +1-800-655-1595  
Fax: +1-651-653-4431

Refer to the lower right-hand corner of Figure 1. The operating component of each Freeze Indicator is a glass capillary tube with a bulb at one end and filled with three fluids located in different segments of the tube: 1) a specially formulated colourless fluid in the bulb, 2) a violet coloured fluid in the capillary stem, and 3) a green coloured fluid in the capillary tube stem that acts as a barrier between the violet and colourless fluids. The bulb fluid is formulated to freeze at 0ºC/32ºF ± 1ºC. The fluids in the Freeze Indicator expand and contract (i.e., move back and forth in the stem of the capillary tube) with temperature variations. As the temperature of exposure decreases, the fluids contract and the green and violet fluids move closer to the glass bulb. When the Freeze Indicator is exposed to temperatures at or below 0ºC/32ºF ± 1ºC, the colourless bulb fluid solidifies and contracts. The reduction in volume of the bulb fluid pulls the coloured fluids into the bulb, and the bulb changes from clear and colourless to cloudy with streaks of violet. If the Freeze Indicator is warmed to a temperature above 0ºC/32ºF, the bulb fluid returns to a liquid state and irreversibly changes to a uniform violet colour (see lower left-hand side of Figure 1).

Figure 1. ColdMark™ 0ºC/32ºF Freeze Indicator
The ColdMark™ 0ºC/32ºF Freeze Indicator has a validated response temperature accuracy of 0ºC ± 1ºC. SkyePharma has performed additional validation work to confirm the response temperature accuracy.

Refer to the top of Figure 1. A closed cell foam piece is placed around the glass stem to secure the position of the stem and also to insulate that portion of the bulb fluid located in the stem. For protection purposes, the glass piece and foam are placed in a package consisting of a thermoformed PVC top cover adhered to a paperboard underside. The overall dimensions of each Freeze Indicator are 3.25 in. x .75 in (8.5 cm x 1.9 cm). The paperboard is coated with a pressure sensitive adhesive covered by a release liner. When the release liner is removed, the adhesive allows attachment of the Freeze Indicator to the inside of the carton lid.

SkyePharma plans to include the following customized text on the top of each freeze indicator: “DO NOT USE PRODUCT IF BULB HAS COLOR.”

Per the manufacturer, the ColdMark™ 0ºC/32ºF Freeze Indicator has a functional shelf life of 3 years. It may be stored at room temperature (not to exceed 43ºC/110ºF) or under refrigeration (2 – 8ºC).
Simulations of plasma concentration – time curves after freezing SKY0401:

As noted in the Effect of Freezing study (Module 3, Section 3.2.P.8.3.9.1, Study Number 03-SS-03), freezing SKY0401 at -20°C for approximately 4 hours resulted in an increase in the percentage of free morphine in the product from an average of 1.5% prior to freezing to 38% after freezing.

The method of superposition was used to determine “the likely plasma concentration – time curve following administration of a 20 mg dose of SKY0401 that has been subjected to freezing.” Mean plasma concentration data from study SKY0401-012B was utilized for the simulation. This trial was a Phase 3, multicenter, randomized, double-blind, dose-controlled, parallel-group, dose-ranging study to evaluate the safety, efficacy, and pharmacokinetic profile of single epidural doses of SKY0401 (5, 10, 15, 20, or 25 mg) compared with unencapsulated morphine (5mg) for the treatment of post-operative pain in patients undergoing lower abdominal surgery. Serum morphine and its metabolites, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G; active metabolite) were determined at multiple time points (predose, 0.25, 0.5, 1, 2, 4, 8, 12, 18, 24, 36, and 48 hours post-dose) during the study in a subset of 68 patients who received active treatment. PK parameters were estimated from serum data for 65 of the 68 patients who had sufficient samples and/or data. The results of this study indicated that the serum pharmacokinetics of morphine were dose-proportional for AUC, and slightly less than dose-proportional for $C_{\text{max}}$, across the dosage range from 5 mg to 25 mg of SKY0401. As a result, using linear superposition to estimate the serum morphine concentrations following SKY0401 is reasonable since it does not require any assumptions concerning the model and the data on dose proportionality indicates that it may, in the worst case, slightly overestimate the $C_{\text{max}}$ values.

Superposition was performed using the mean serum concentration versus time profile for the 11 patients who received unencapsulated morphine 5 mg and the 12 patients who received 20 mg of SKY0401. The superposition was conducted under the assumption that freezing would create a situation where the \textit{in vivo} absorption of morphine approximates the simultaneous administration of an unencapsulated morphine dose and a SKY0401 dose. Using the results of the freeze-thaw study it was determined that the mean “free-morphine” concentration in the product was 1.5% prior to freezing and 38% after a freeze-thaw cycle. Therefore, we assumed that 36.5% of the dose (38% free after freezing - 1.5% free before freezing) would have an absorption profile like unencapsulated morphine and the remaining 63.5% of the dose would have an absorption profile like SKY0401. As a result, the plasma concentration versus time profile resulting from a 20 mg SKY0401 dose that had been subjected to freezing would be the same as simultaneous administration of a 7.3 mg dose of unencapsulated morphine with a 12.7 mg dose of SKY0401. The “worst case” scenario assumed that 100% of the dose would be absorbed like unencapsulated morphine.

Concentrations that were < the lower limit of quantitation for the study (reported as 0.000 ng/mL) were replaced with extrapolated values ($C_n$) calculated using the following equation:

$$C_n = C_{n-1} \cdot e^{-k_e(t_n - t_{n-1})}$$
Where $k_e$ is the elimination rate constant calculated from the average serum concentration versus time curve. Calculated concentrations were rounded to the nearest 0.001 ng/mL. The serum morphine concentrations likely to occur following administration of a 20 mg SKY0401 dose that has been frozen are displayed in Figure 2 (below) and summarized in Table 3 (next page).

**Figure 2: Simulated Average Morphine Plasma Concentrations**

![Graph showing simulated average morphine plasma concentrations over time for 20 mg Frozen, 20 mg Unencapsulated, and 20 mg SKY0401 doses.]

**Table 3: Simulated Average Morphine Plasma Concentrations**

<table>
<thead>
<tr>
<th>Time</th>
<th>20 mg Frozen [1]</th>
<th>20 mg Unencapsulated</th>
<th>20 mg SKY0401 [3]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>0.25</td>
<td>49.124</td>
<td>100.460</td>
<td>19.616</td>
</tr>
<tr>
<td>0.5</td>
<td>25.419</td>
<td>52.820</td>
<td>9.669</td>
</tr>
<tr>
<td>1</td>
<td>20.281</td>
<td>34.752</td>
<td>11.963</td>
</tr>
<tr>
<td>2</td>
<td>16.985</td>
<td>25.564</td>
<td>12.053</td>
</tr>
<tr>
<td>4</td>
<td>11.993</td>
<td>12.648</td>
<td>11.616</td>
</tr>
<tr>
<td>8</td>
<td>5.253</td>
<td>4.092</td>
<td>5.920</td>
</tr>
<tr>
<td>12</td>
<td>2.480</td>
<td>0.712</td>
<td>3.496</td>
</tr>
<tr>
<td>18</td>
<td>1.129</td>
<td>0.034</td>
<td>1.759</td>
</tr>
<tr>
<td>24</td>
<td>0.722</td>
<td>0.002</td>
<td>1.136</td>
</tr>
<tr>
<td>36</td>
<td>0.486</td>
<td>0.000</td>
<td>0.765</td>
</tr>
<tr>
<td>48</td>
<td>0.295</td>
<td>0.000</td>
<td>0.465</td>
</tr>
</tbody>
</table>

[1] determined using superposition, 7.3 mg unencapsulated + 12.7 mg SKY0401
[2] calculated using linear extrapolation from 5 mg dose
[3] observed mean plasma concentrations, Study SKY0401-012B
Based on the superposition results, it is estimated that the average peak morphine concentration is increased approximately 2.5-fold relative to the observed SKY0401 peak concentrations (from 19.161 ng/mL to 49.124 ng/mL) as a result of freezing (simulation of the results observed in vitro). If extended freezing were to cause a complete release of morphine from the liposomal matrix, the peak serum concentrations could be expected to approximate those associated with a 20 mg dose of unencapsulated morphine. In that event, the worst case effect of freezing SKY0401 would be to increase peak morphine levels by approximately 5-fold over the controlled-release dose (from 19.161 ng/mL to 100.460 ng/mL).

**Assessor’s comment**

The proposal to include a freeze indicator in each carton of SKY0401 is welcomed. The pharmaceutical assessor has advised on the technical adequacy of the proposed system.

The PK modelling appears reasonable and is broadly in line with data elsewhere in the dossier on the PK characteristics for unencapsulated morphine and Depodur given epidurally. The proposed usual 20mg dose of Depodur if it had been inadvertently frozen would produce an estimated plasma Cmax 2.5 times higher than it should be, and comparable to that which would follow unencapsulated morphine 10mg given epidurally or intramuscularly. 10mg of morphine intramuscularly is a therapeutic dose. The worst case scenario of complete destruction of the release controlling mechanism would produce an estimated plasma Cmax be equivalent to approximately 20mg morphine intramuscularly (normal adult dose 10-15mg i.m.). In terms of systemic exposure there is unlikely to be a major safety problem.

There are greater concerns about CSF levels. The implications for drug levels in the CSF at various levels and hence for the danger of late respiratory depression is unclear and unquantifiable. Presumably the risk would be substantially increased if the product were frozen prior to administration resulting in 2.5 times greater CSF levels. The clinical safety data appear to show a greater risk of late respiratory depression in patients who were given doses up to 1.5 times higher than the company is currently proposing (25mg or 30mg instead of 20mg).

The freeze indicator is therefore important.

It has been proposed that the freeze indicator will carry the text “DO NOT USE PRODUCT IF BULB HAS COLOR”. The English spelling of ‘colour’ should be used and it would be preferable to replace ‘HAS COLOR’ with ‘IS COLOURED’.

The pharmaceutical assessor confirms that the proposed system is technically satisfactory and this point may be considered cleared.

**Point cleared**
Following the Hearing on 31 March 2005, in which the additional documentation was considered, the Committee were not reassured by the data presented on the safety concerns relating to delayed respiratory depression in the context of routine post-operative care in an environment such as a general surgical ward. The Committee did however consider that the risk-benefit would be positive in the context of High Dependency monitoring for 48 hours following administration of Depodur, which is the period during which there might be a risk of serious delayed respiratory depression. The Committee determined additional and amended SPC wording that will need to be adopted in order for it to be able to advise the grant of a marketing authorisation for this preparation.

The Committee considered that a pharmacovigilance risk management plan must be agreed with the MHRA prior to the grant of a marketing authorisation.

The following medical point required satisfactory resolution before Committee Marketing Authorisations could be granted:

**Medical Point:**

*Pharmacokinetics*

Whilst it is accepted that the overall pharmacokinetics of the products as demonstrated in the clinical programme have been discussed in the original dossier, a stand-alone response should be provided that addresses the lack of dose proportionality in $C_{\text{max}}$ values. The response should include discussion of the physical stability of the product, the free morphine content and the in vivo release characteristics. (Arises from Point 50 of the CSM letter dated 01 July 2004).

Further documentation was received from the applicant and the medical assessors comments are noted below:

**Company response:**

Pharmacokinetic parameters from the pooled analysis from Section 2.7.2 of the MAA are presented in the table below. The pooled analysis includes pharmacokinetic data from the following six clinical studies: DTC96-003, SKY0401-008, SKY0401-009, SKY0401-011, SKY0401-012, and SKY0401-016.
Morphine Plasma Pharmacokinetic Parameters (Mean, SD) Following Epidural Administration of SKY0401: Pooled Analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SKY0401 5 mg (n=14)</th>
<th>SKY0401 10 mg (n=36)</th>
<th>SKY0401 15 mg (n=71)</th>
<th>SKY0401 20 mg (n=63)</th>
<th>SKY0401 25 mg (n=32)</th>
<th>SKY0401 30 mg (n=25)</th>
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<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
<td>9.4 (5.7)</td>
<td>20.0 (9.5)</td>
<td>18.6 (10.4)</td>
<td>26.4 (18.6)</td>
<td>22.6 (15.4)</td>
<td>47.3 (28.9)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-τ&lt;/sub&gt; (ng•hr/ml)</td>
<td>30.9 (11.8)</td>
<td>135.9 (116.7)</td>
<td>100.9 (43.6)</td>
<td>160.8 (76.3)</td>
<td>158.3 (55.7)</td>
<td>297.9 (134.8)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (ng•hr/ml)</td>
<td>41.0 (10.6)</td>
<td>124.9 (98.1)</td>
<td>131.6 (73.7)</td>
<td>185.9 (81.4)</td>
<td>207.3 (77.7)</td>
<td>341.5 (136.9)</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (hr)</td>
<td>4.2 (2.1)</td>
<td>16.2 (19.7)</td>
<td>20.0 (20.6)</td>
<td>23.9 (25.4)</td>
<td>32.9 (24.2)</td>
<td>25.6 (14.6)</td>
</tr>
<tr>
<td>CL/F (ml/min/kg)</td>
<td>28.9 (9.7)</td>
<td>23.3 (13.5)</td>
<td>31.1 (21.8)</td>
<td>27.7 (12.1)</td>
<td>27.4 (10.6)</td>
<td>22.4 (8.8)</td>
</tr>
<tr>
<td>Vz/F (l/kg)</td>
<td>9.9 (3.8)</td>
<td>24.2 (26.6)</td>
<td>38.2 (28.2)</td>
<td>46.3 (40.2)</td>
<td>62.0 (31.2)</td>
<td>42.9 (16.7)</td>
</tr>
</tbody>
</table>

Although we stated in the dossier that the AUCs appeared to be linear with dose but that the C<sub>max</sub> values were not, the graphical presentation of this data on the next page suggests that, considering the subject-to-subject variability (i.e., the wide standard deviations), a firm conclusion as to the lack of dose-proportionality of the C<sub>max</sub> data is probably not warranted.

With regard to the physical properties (including free morphine content, stability, etc.) of the product and their effect on the in vivo release characteristics, the analysis provided in the response to Question 9 provides significant insight. An increase in free morphine up to the limit of 9% resulting during storage under recommended conditions over the shelf-life of the product, coupled with small increases (1–3%) resulting from dilution (up to 1:5) and passage of the product through a syringe has minimal effect on the expected pharmacokinetic behaviour, especially considering the subject-to-subject variability observed in the clinical studies.
Assessors comment

This is a satisfactory response. Pharmacokinetic points are cleared.

CONCLUSION

All changes requested by the UK Advisory committee were made and final product particulars were supplied and approved. Marketing authorisations for Depodur Suspension for Injection (10mg/1ml, 15mg/1.5ml and 20mg/2ml) were granted on 20th April 2006.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Depodur Suspension for Injection are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
Since the properties of morphine are well established, the nonclinical programme focused on demonstrating that morphine is actually released from DepoFoam™ and that Depodur Suspension for Injection is likely to be safe when used for epidural injection.

Results of the toxicology studies did not identify any properties likely to cause toxicity in humans when the product is used as directed in the SPC.

EFFICACY
The product is intended to be given as a single epidural injection to provide post-operative pain relief for up to 48 hours.

Morphine Sulphate is a well-known drug and has been used as an analgesic for many years. Depodur Suspension for Injection has been shown to provide effective pain relief following a single epidural injection and produces significantly more prolonged analgesia than can be achieved with unencapsulated epidural morphine.

No clinically significant safety concerns arise from these applications provided that patients receive high dependency monitoring for 48 hours following administration of the product.

The SPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable, no significant preclinical or clinical safety concerns were identified. Extensive clinical experience with morphine sulphate is considered to have demonstrated the therapeutic value of the compound. Clinical data supplied with these applications has demonstrated the safety and efficacy of Depodur Suspension for injection when given as a single epidural injection under conditions specified in the SPC. The risk benefit is therefore considered to be positive.
DEPODUR SUSPENSION FOR INJECTION

PL20334/0002-4

STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the marketing authorisation application for Depodur Suspension for Injection on 24/11/2003

2. Following standard checks the MHRA informed the applicant that its application was considered valid on 01/12/2003

3. The MHRA’s assessment of the submitted data was completed on 27/05/2004

4. The MHRA’s assessment report was considered by the Committee on Safety of Medicines (CSM) on 24/06/2004

5. The applicant was informed that CSM could not recommend the granting of marketing authorisation on 01/07/2004

6. The applicant appealed against the CSM decision and presented additional information on 10/09/2004

7. The MHRA’s assessment report was considered by the Chemistry, Pharmacy and Standards Sub-committee (CPS) on 16/02/2005.

8. The MHRA’s assessment of the appeal data was presented to CSM on 31/03/2005

9. The applicant was informed that CSM recommended approval of the application subject to the successful resolution of outstanding points and amendments to the product particulars (SPC, PIL and labelling) on 20/04/2005


11. The MHRA completed its assessment of the updated product particulars on 24/03/2006.

12. The application was determined on 21/04/2006
# DEPODUR SUSPENSION FOR INJECTION

**PL20334/0002-4**

## STEPS TAKEN AFTER ASSESSMENT

<table>
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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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</table>
1. NAME OF THE MEDICINAL PRODUCT
Depodur 10 mg/1 ml Suspension for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 10mg/1 ml morphine sulfate pentahydrate.
For excipients, see Section 6.1

3. PHARMACEUTICAL FORM
Suspension for Injection
White to off-white homogeneous suspension

4. CLINICAL PARTICULARS

4.1. Therapeutic indications
For the relief of post-operative pain following major orthopaedic, abdominal or pelvic surgery.

4.2. Posology and method of administration
Depodur is only for epidural administration. Intravenous, intramuscular, and intrathecal administrations are contraindicated. Experience of Depodur in clinical trials has been limited to patients assessed as ASA grade I to III. Depodur is not recommended in patients graded ASA IV or V. Depodur may be administered peri-operatively via needle or catheter at the lumbar or lower thoracic levels. Administration of Depodur at the mid-thoracic level or higher has not been studied. Depodur may be administered undiluted or diluted up to 5-ml total volume with preservative-free 0.9% normal saline.
Continuous monitoring and observation of the patient for 48 hours following administration of Depodur is mandatory in order to identify possible respiratory depression, which may be delayed, profound and of sudden onset (see sections 4.4 and 4.8). The minimum level of monitoring includes pulse oximetry, cardiac ECG monitoring and continuous observation and/or monitoring of respiratory rate, in a
suitable environment with appropriately trained staff. During this period, full resuscitation facilities must be immediately available, including staff trained in airway management and artificial ventilation. A single dose of Depodur should be considered to be equivalent to a continuous epidural infusion of morphine, and attendant monitoring requirements must reflect this, in line with relevant guidelines.

NB Continuous, close monitoring of patients for 48 hours after receiving Depodur is mandatory irrespective of whether planned surgery was subsequently cancelled or modified.

**Adults and the elderly**

For major orthopaedic surgery of the lower extremity, the recommended dose of Depodur is 15 mg.

For lower abdominal or pelvic surgery, the recommended dose of Depodur is 10 – 15 mg.

Some patients may benefit from a 20 mg dose of Depodur. However, the incidence of serious adverse events, including delayed respiratory depression, was dose-related in clinical trials.

For caesarean section, the recommended dose of Depodur is 10 mg (n.b. contraindicated in patients who have received epidural local anaesthetics for analgesia during labour – see sections 4.3 and 4.5.)

For operations associated with less severe pain and/or where freedom from the usual side effects of morphine is a priority, and in elderly, frail or debilitated patients, lower doses may suffice. The maximum recommended dose in elderly patients (≥ 65 years) is 15 mg.

Depodur should only be administered by or under the direction of a physician experienced in epidural administration of opioids, and only where there are immediate facilities for resuscitation, including staff trained in airway management and artificial ventilation.

Before administration of Depodur, the physician must ensure that the needle or catheter is properly placed in the epidural space. Techniques to exclude misplacement of the needle or catheter include aspiration to check that blood or cerebrospinal fluid cannot be aspirated and administration of a test dose of local anaesthetic with epinephrine. If a test dose is administered, in order to minimise a pharmacokinetic interaction of Depodur, the epidural catheter should be flushed with 1 ml of preservative-free 0.9% normal saline, and Depodur should not be administered for at least a further 10 minutes (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Rescue analgesia may be required. The use of concomitant systemic opioids may increase the risk of serious adverse events (see section 4.4).
Do not mix Depodur with any other medications. Once Depodur has been administered, no other medication should be administered into the epidural space for at least 48 hours.

Because Depodur consists of lipid-based particles, an in-line filter must not be used during administration of Depodur.

Protect Depodur from freezing. Freezing may cause the modified release mechanism to fail. Do not administer Depodur if the freeze indicator in the carton shows colouration or if it is otherwise suspected that the vial may have been frozen (see section 4.4).

The outer cartons contain 5 vials. A freeze indicator that is visible through the top of the carton indicates exposure to a temperature below 0°C. It is important that the freeze indicator is inspected before removal of a vial from the carton. Vials from this carton should only be used if the solution in the bulb of the freeze indicator is clear. If the solution in the bulb is coloured, then the product should be destroyed.

Vials of Depodur should be gently inverted to re-suspend the particles immediately prior to withdrawal from the vial. Avoid aggressive agitation. No further reconstitution or dilution is required.

Depodur is a sterile agent; however, it does not contain any bacteriostatic agents. From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately. Do not heat-sterilize or gas-sterilize.

Discard any unused portion in a manner appropriate for controlled drugs.

**Paediatrics**

The safety and effectiveness of Depodur in patients below the age of 18 years has not been established.

**4.3. Contraindications**

Depodur is contraindicated in patients with known hypersensitivity to morphine, morphine salts, or any components of the product.

Depodur is contraindicated in patients receiving concurrent epidural anaesthesia, as local anaesthetics may cause the modified release mechanism to fail, resulting in overdose (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Depodur, like all opioids, is contraindicated in patients with respiratory depression, acute or severe bronchial asthma, or upper airway obstruction, unless elective post-operative mechanical ventilation is planned.

Depodur, like all opioids, is contraindicated in any patient who has or is suspected of having paralytic ileus.
Any contraindications for an epidural injection preclude the administration of Depodur.

4.4. Special warnings and precautions for use

Delayed respiratory depression is a potentially life threatening complication following epidural administration of opioids, especially hydrophilic agents such as morphine. It has been reported in patients who have received Depodur (see section 4.8). Continuous close monitoring and immediate availability of full resuscitation facilities is mandatory for a period of 48 hours following administration of Depodur (see section 4.2).

The action of Depodur persists for up to 48 hours. Respiratory depression can be severe if surgical pain is limited or absent. Extreme care must be taken if Depodur is given and surgery is subsequently cancelled or changed to a more minor procedure, or if alternative or additional analgesic techniques are used.

Systemic opioids may increase the risk of serious adverse events including respiratory depression. Particular caution is necessary with opioid agents of an intermediate or prolonged duration of action. Short acting agents may be more suitable if analgesic supplements are needed.

No clinical studies have evaluated the safety of administration of Depodur into the intrathecal space. Studies in dogs administered Depodur intrathecally demonstrated no toxicity attributable to the lipid component of Depodur. While the adverse effects observed in these dogs were typical opioid side effects consistent with the dose of morphine administered, profound and prolonged respiratory depression would be expected in humans.

Prior to drug administration, the physician should be familiar with patient conditions (such as infection at the injection site, bacteraemia, bleeding diathesis, current and anticipated anticoagulant therapy, etc.) that call for special evaluation of the benefit versus risk potential.

Use with caution in opiate-dependent patients and in patients with decreased pulmonary function, raised intracranial pressure, hypotension with hypovolaemia, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, prostatic hypertrophy, sleep apnoea, and adrenocortical insufficiency.

In addition, Depodur may cause hypotension, paralytic ileus, urinary retention, biliary colic, somnolence, pruritis, nausea, and vomiting.

Protect Depodur from freezing. Do not administer Depodur if it is suspected that the vial has been frozen, as this may cause the modified release mechanism to fail, resulting in overdose and an increased risk of serious adverse events (see section 4.2).

Depodur contains less than 1 mmol sodium (23 mg) per 10 ml.
4.5. Interactions with other medicinal products and other forms of interaction

Local Anaesthetics: Clinical studies have demonstrated that administration of Depodur three minutes after a 3-ml test-dose (lidocaine 1.5% and adrenaline 1:200,000) increases peak serum concentrations of morphine. Increasing the interval between the test dose and Depodur administration to at least 10 minutes minimises this pharmacokinetic interaction. Please see the dosage recommendations in Section 4.2 in respect of this interaction and note the contraindication in patients receiving concurrent epidural anaesthesia (Section 4.3).

Other than the interaction with a lidocaine plus adrenaline test-dose described above, no other pharmacokinetic drug-drug interactions have been examined in vivo. In vitro studies suggest a similar interaction could be expected with other amide local anaesthetics. No in vitro or in vivo studies have been performed with ester-type local anaesthetics. Known drug-drug interactions involving morphine are pharmacodynamic, not pharmacokinetic.

Concurrent systemic or spinal administration of α2 agonists (e.g. clonidine) may potentiate opioid analgesia. Pharmacodynamic and pharmacokinetic interactions between Depodur and neuraxially or systemically administered α2 agonists were not evaluated. Therefore, concomitant use of these drugs should not be attempted.

CNS Depressants: The concurrent use of other central nervous system (CNS) depressants including sedatives, hypnotics, general anaesthetics, droperidol, phenothiazines, or other tranquilizers or alcohol increases the risk of respiratory depression, hypotension, profound sedation, or coma. Use with caution and in reduced dosages in patients taking these agents.

Monoamine Oxidase Inhibitors (MAOIs): MAOIs markedly potentiate the action of morphine. Depodur should not be used in patients taking MAOIs or within 14 days of stopping such treatment.

4.6. Pregnancy and lactation

Depodur should not be administered to women during pregnancy, though it may be administered following clamping of the umbilical cord as part of the anaesthetic technique for caesarean section where facilities for post-operative monitoring are available (see section 4.2).

In studies of epidural administration of morphine sulfate injection, small amounts of morphine were detected in breast milk.

4.7. Effects on ability to drive and use machines

Depodur, in common with other opioids, has CNS depressant effects. Effects on the ability to drive or operate machinery have not been studied, but it is expected to have a major influence on the ability to drive or operate machines within 48 hours.
of administration. Patients should not drive or use heavy machinery until all adverse CNS effects have fully worn off.

4.8. Undesirable effects

The most common adverse events (greater than 10%) reported during therapy in patients treated with Depodur were nausea, pruritus, pyrexia, vomiting, hypotension, anaemia, headache, constipation, respiratory depression, decreased oxygen saturation, urinary retention, and dizziness. Adverse events occurring in 5-10% of study patients were flatulence, tachycardia, insomnia, and hypoxia. Other less common side effects (seen in 2-5% of patients receiving Depodur) included somnolence, abdominal distension, hypoesthesia, hypertension, oliguria, bradycardia, anxiety, back pain, increased sweating, dyspepsia, bladder spasm, rigors, hypercapnia, dyspnoea, hypokalaemia, ileus paralytic, paraesthesia, and decreased haematocrit.

Delayed respiratory depression, which may be of sudden onset and is potentially life threatening, occurred up to 48 hours post dosing in approximately 2% of patients who have received Depodur.

4.9. Overdose

Overdosage of morphine is characterised by respiratory depression, with or without concomitant CNS depression. Since respiratory arrest may result either through direct depression of the respiratory centre or as the result of hypoxia, primary attention should be given to the establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. The opioid antagonist, naloxone, is a specific antidote. An initial dose of 0.04 to 2 mg of naloxone should be administered intravenously, simultaneously with respiratory resuscitation. Doses at the lower end of this range may reverse unwanted effects including (non-delayed) respiratory depression without reversing the analgesia produced by epidural morphine. Higher doses may also reverse analgesia. If the desired degree of counteraction and improvement in respiratory function is not obtained, naloxone may be repeated at 2- to 3-minute intervals. If no response is observed after 10 mg of naloxone has been administered, the diagnosis of opioid-induced, or partial opioid-induced, toxicity should be questioned. Intramuscular or subcutaneous administration of naloxone may be used if the intravenous route is not available.

As the duration of effect of naloxone is considerably shorter than that of Depodur, repeated administration or continuous infusion of naloxone may be necessary. Patients should be closely observed for evidence of recurrence of respiratory depression and for delayed respiratory depression.

5. PHARMACOLOGICAL PROPERTIES
5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloid
ATC Code: N02A 01

Morphine acts as an agonist at opiate receptors in the CNS, particularly mu and, to a lesser extent, kappa receptors. Mu receptors are thought to mediate supraspinal analgesia, respiratory depression, and euphoria, and kappa receptors, spinal analgesia, miosis, and sedation. Morphine also has a direct action on the bowel wall nerve plexuses, causing constipation.

Epidural administration of morphine sulfate results in analgesia without attendant loss of motor, sensory, or sympathetic function. As compared to systemic administration of morphine at comparable doses, epidurally administered morphine results in improved analgesia with increased duration.

Depodur is a sustained-release formulation of the active ingredient morphine sulfate designed for epidural administration. Morphine released from Depodur is absorbed both neuraxially and systemically.

5.2. Pharmacokinetic properties

Epidural administration of Depodur results in both systemic absorption of morphine sulfate and absorption of morphine sulfate through the meninges into the intrathecal space. The relative absorption systemically versus intrathecally is unknown for both morphine sulfate injection and for Depodur.

Systemic Absorption of Morphine from Depodur

Relative systemic bioavailability of Depodur compared to epidurally administered morphine sulfate injection was determined in 21 patients (Table 1).

Table 1: Pharmacokinetics of Depodur and Morphine Sulfate Injection (Mean +/- SD)

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Depodur 5 mg (n = 10)</th>
<th>Mean</th>
<th>SD</th>
<th>Morphine sulfate injection 5 mg (n = 11)</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>7.10</td>
<td>3.40</td>
<td></td>
<td>25.35</td>
<td>12.01</td>
<td></td>
</tr>
<tr>
<td>$t_{\text{max}}$ (hr)$^1$</td>
<td>1.00</td>
<td>4.0</td>
<td>0.25-</td>
<td>0.25</td>
<td>2.0</td>
<td>0.25-</td>
</tr>
<tr>
<td>AUC (ng•hr/ml)</td>
<td>38.80</td>
<td>10.35</td>
<td></td>
<td>44.07</td>
<td>7.95</td>
<td></td>
</tr>
<tr>
<td>$t_{1/2}$ (hr)</td>
<td>3.82</td>
<td>1.00</td>
<td></td>
<td>2.25</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>AUC$^2$</td>
<td>37.41</td>
<td></td>
<td></td>
<td>43.48</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^1$ Median (range)
$^2$ Geometric mean of the log-transformed variables used to calculate bioavailability
Depodur was 89% bioavailable compared to morphine sulfate injection and demonstrated dose proportionality over a dose range of 5 to 25 mg.

**Distribution, Metabolism, and Excretion of Morphine Sulfate**
After morphine sulfate has been released from Depodur and is absorbed systemically, its distribution, metabolism and excretion are the same as other morphine formulations. Depodur is intended for single dose administration; therefore accumulation of morphine or its metabolites is not expected even in patients with impaired hepatic or renal function.

5.3. **Preclinical safety data**
Preclinical data reveal no special hazard for humans based on conventional toxicology studies.

6. **PHARMACEUTICAL PARTICULARS**

6.1. **List of excipients**
- Dioleoylphosphatidylcholine
- Dipalmitoylphosphatidylglycerol
- Cholesterol
- Triolein
- Tricaprylin
- Sodium chloride
- Diluted (10%) hydrochloric acid
- Water for injections

6.2. **Incompatibilities**
Do not mix Depodur with any other medications. Once Depodur has been administered, no other medication should be administered into the epidural space for at least 48 hours.

6.3. **Shelf life**
2 years
From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately.

6.4. **Special precautions for storage**
Store in a refrigerator (2° to 8°C).
Do not freeze. Where there is evidence or suspicion that Depodur has been frozen, it should be disposed of in the way specified for opioid drugs.
Avoid aggressive shaking.

Keep the vials in the outer carton. The outer cartons contain 5 vials. A freeze indicator that is visible through the top of the carton indicates exposure to a temperature below 0°C. It is important that the freeze indicator is inspected before removal of a vial from the carton. Vials from this carton should only be used if the solution in the bulb of the freeze indicator is clear. If the solution in the bulb is coloured, then the product should be destroyed.

Depodur may be held for up to 7 days at up to 25°C in sealed, intact (unopened) vials.

6.5. Nature and contents of container

Depodur is available in 10mg/1 ml single-use, Type I amber glass vials with ethylenetetrafluoroethylene (ETFE) stoppers and aluminium caps. Pack sizes are as follows:

10mg/1ml vials packaged in cartons of 5

6.6. Instructions for use and handling and disposal

Depodur consists of morphine encapsulated in multivesicular lipid-based particles that pose no known risk of handling to health care workers.

Each vial of Depodur contains a potent opioid that has been associated with abuse and dependence among health care providers. Appropriate measures should be taken to control this product within the hospital or clinic including rigid accounting, rigorous control of wastage, and restricted access.

7. MARKETING AUTHORISATION HOLDER
8. MARKETING AUTHORISATION NUMBER

PL 20334/0002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/04/2006

10. DATE OF REVISION OF THE TEXT

20/04/2006
1. NAME OF THE MEDICINAL PRODUCT

Depodur 15 mg/1.5 ml Suspension for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 15mg/1.5 ml morphine sulfate pentahydrate.

For excipients, see Section 6.1

3. PHARMACEUTICAL FORM

Suspension for Injection

White to off-white homogeneous suspension

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

For the relief of post-operative pain for up to 48 hours.

4.2. Posology and method of administration

Adults and the elderly
Depodur is intended only for epidural administration. Intravenous, intramuscular and intrathecal administration are contraindicated. Depodur may be administered peri-operatively via needle or catheter at the lumbar and lower thoracic levels, except in caesarean section (see below). Administration of Depodur at the mid-thoracic level or higher has not been studies. Depodur may be administered undiluted or may be diluted up to 5ml total volume with preservative-free 0.9% normal saline.

Table 1: Dosing Recommendations by Surgery Type and Patient Age

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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 65 years</td>
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MHRA PAR - Depodur Suspension for Injection PL20334/0002-4 - 90 -
Depodur has been administered to women undergoing caesarean section following clamping of the umbilical cord. Depodur should not be administered to women for vaginal labour and delivery.

Depodur should be administered by or under the direction of a physician experienced in the technique of epidural administration and who is thoroughly familiar with the labelling of this product.

Improper placement of a needle or catheter in the epidural space should be ruled out before Depodur is injected. Acceptable techniques to rule out improper placement of a needle or catheter include: a) aspiration to check for absence of blood or cerebrospinal fluid and/or b) administration of 3ml of 1.5% preservative-free lidocaine and adrenaline (1:200,000) test dose. If a test dose is administered, observe the patient for lack of tachycardia (this indicates that vascular injection has not occurred) and lack of segmental anaesthesia (this indicates that intrathecal administration has not occurred). To minimise a pharmacokinetic interaction of Depodur with the test dose, flush the catheter/needle with 1ml of preservative-free 0.9% normal saline and wait for at least 10 minutes after administration of the test dose before administering Depodur.

Do not mix Depodur with any other medications. Once Depodur has been administered, no other medication should be administered into the epidural space for at least 48 hours.

Do not use an in-line filter during administration of Depodur.

Depodur is a sterile agent; however, it does not contain any bacteriostatic agents. Therefore, Depodur must be administered within 4 hours after withdrawal from the vial. Do not heat-sterilise or gas-sterilise.

Discard any unused portion in a manner appropriate for controlled drugs.

Protect Depodur from freezing. Do not administer Depodur if it is suspected that the vial has been frozen.

**Paediatrics**
The safety and effectiveness of Depodur in paediatric patients below the age of 18 years has not yet been established.

### 4.3. Contraindications

Depodur is contraindicated in patients with known hypersensitivity to morphine, morphine salts, or any components of the product. Depodur, like all opioids, is contraindicated in patients with respiratory depression, acute or severe bronchial asthma, or upper airway obstruction. Any contraindications for an epidural injection

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<thead>
<tr>
<th>Procedure</th>
<th>Dose</th>
<th>Morphine</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip and knee orthopaedic</td>
<td>20mg</td>
<td>15mg</td>
<td></td>
</tr>
<tr>
<td>Lower abdominal</td>
<td>20mg</td>
<td>15mg</td>
<td></td>
</tr>
<tr>
<td>Caesarean section</td>
<td>10mg</td>
<td>N/A</td>
<td></td>
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4.4. Special warnings and precautions for use

No clinical studies have evaluated the safety of administration of Depodur into the intrathecal space. Studies in dogs administered Depodur intrathecally demonstrated no toxicity attributable to the lipid component of Depodur. While the adverse effects observed in these dogs were typical opioid side effects consistent with the dose of morphine administered, profound and prolonged respiratory depression would be expected in humans.

Prior to drug administration, the physician should be familiar with patient conditions (such as infection at the injection site, bleeding diathesis, current and anticipated anticoagulant therapy etc.) that call for special evaluation of the benefit versus risk potential.

Use with caution in opiate-dependent patients and patients with decreased pulmonary function, raised intracranial pressure, hypotension with hypovolaemia, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, prostatic hypertrophy, sleep apnoea, and adrenocortical insufficiency.

Respiratory depression is of particular concern for all epidural opioid preparations. If the surgical procedure is cancelled after the administration of Depodur, the risk of respiratory depression may be increased because of the missing pain stimulus. Because of the risk of respiratory depression, the facility must be equipped to resuscitate patients. Patients must be closely monitored in a fully equipped and staffed environment for at least 24 hours after Depodur administration with additional monitoring for an additional 24 hours, especially if the surgical procedure was after administration of Depodur.

In addition, Depodur may cause hypotension, paralytic ileus, urinary retention, biliary colic, somnolence, pruritis, nausea and vomiting.

4.5. Interactions with other medicinal products and other forms of interaction

Local anaesthetics: Clinical studies have demonstrated that administration of Depodur three minutes after a 3ml test-dose (lidocaine 1.5% and adrenaline 1:200,000) increases peak serum concentrations of morphine. However, no clinically meaningful effects on safety or efficacy were observed, despite the administration of such a test dose. Increasing the interval between the test dose and Depodur administration to at least 10 minutes minimises this pharmacokinetic interaction. Please see the dosage recommendations in Section 4.2 in respect of this interaction.

Other than the interaction with a lidocaine plus adrenaline test-dose described above, no other pharmacokinetic drug-drug interactions have been examined in vivo. In vitro studies suggest a similar interaction could be expected with other
amide local anaesthetics. No *in vitro* or *in vivo* studies have been performed with ester local anaesthetics. Known drug-drug interactions involving morphine are pharmacodynamic, not pharmacokinetic.

CNS Depressant: The concurrent use of other central nervous system (CNS) depressants including sedatives, hypnotics, general anaesthetics, droperidol, phenothiazines, or other tranquillisers or alcohol increases the risk of respiratory depression, hypotension, profound sedation, or coma. Use with caution and in reduced dosages in patients taking these agents.

Monoamine Oxidase Inhibitors (MAOIs): MAOIs markedly potentiate the action of morphine. Depodur should not be used in patients taking MAOIs or within 14 days of stopping such treatment.

### 4.6. Pregnancy and lactation

Depodur should not be administered to women during pregnancy, though it may be used during delivery by caesarean section. See section 4.2

In studies of epidural administration of morphine sulfate injection, small amounts of morphine were detected in breast milk.

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

Depodur, in common with other opioids, has CNS depressant effects. Effects on the ability to drive or operate machinery have not been studied, but it is expected to have a major influence on the ability to drive or operate machines within 48 hours of administration. Therefore, patients should not drive or use heavy machinery within 48 hours of administration.

### 4.8. Undesirable effects

The most common adverse events (greater than 10%) reported during therapy in patients treated with Depodur were nausea, pruritis, pyrexia, vomiting, hypotension, anaemia, headache, constipation, decreased oxygen saturation, urinary retention and dizziness. Adverse events occurring in 5 – 10% of study patients were flatulence, tachycardia, insomnia and hypoxia. Other less common side-effects (seen in 2-5% of patients receiving Depodur) included somnolence, abdominal distension, hypoesthesia, hypertension, respiratory depression, oliguria, bradycardia, anxiety, back pain, increased sweating, dyspepsia, bladder spasm, rigors, hypercapnia, dyspnoea, hypokalaemia, ileus paralytic, paresthesia and decreased haematocrit.

### 4.9. Overdose

Overdosage of morphine is characterised by respiratory depression, with or without concomitant CNS depression. Since respiratory arrest may result either through
direct depression of the respiratory centre or as a result of hypoxia, primary attention should be given to the establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. The opioid antagonist, naloxone, is a specific antidote. An initial dose of 0.4 to 2mg of naloxone should be administered intravenously, simultaneously with respiratory resuscitation. If the desired degree of counteraction and improvement in respiratory function is not obtained, naloxone may be repeated at 2 to 3 minute intervals. If no response is observed after 10mg of naloxone has been administered, the diagnosis of opioid-induced, or partial opioid-induced, toxicity should be questioned. Intramuscular or subcutaneous administration of naloxone may be used if the intravenous route is not available.

As the duration of effect of naloxone is considerably shorter than that of Depodur, repeated administration or continuous infusion of naloxone may be necessary. Patients should be closely observed for evidence of recurrence of respiratory depression.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloid
ATC Code: N02A 01

Morphine acts as an agonist at opiate receptors in the CNS, particularly mu and, to a lesser extent, kappa receptors. Mu receptors are thought to mediate supraspinal analgesia, respiratory depression, and euphoria, and kappa receptors, spinal analgesia, miosis, and sedation. Morphine also has a direct action on the bowel wall nerve plexuses, causing constipation.

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5.2. Pharmacokinetic properties

Epidural administration of Depodur results in both systemic absorption of morphine sulfate and absorption of morphine sulfate through the meninges into the intrathecal space. The relative absorption systemically versus intrathecally is unknown for both morphine sulfate injection and for Depodur.

Systemic Absorption of Morphine from Depodur
Relative systemic bioavailability of Depodur compared to epidurally administered morphine sulfate injection was determined in 21 patients (Table 2).

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<th>Depodur 5mg (n = 10)</th>
<th>Morphine sulfate Injection 5mg (N = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_max (ng/ml)</td>
<td>Mean: 7.10, SD: 3.40</td>
<td>Mean: 25.35, SD: 12.01</td>
</tr>
<tr>
<td>T_max (hr)</td>
<td>1.00 (0.25 – 4.0)</td>
<td>0.25 (0.25 – 2.0)</td>
</tr>
<tr>
<td>AUC (ng.hr/ml)</td>
<td>38.80, 10.35</td>
<td>44.07, 7.95</td>
</tr>
<tr>
<td>t_1/2 (hr)</td>
<td>3.82, 1.00</td>
<td>2.25, 0.45</td>
</tr>
<tr>
<td>AUC^2</td>
<td>37.41</td>
<td>43.48</td>
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</table>

1 Median (range)
2 Geometric mean of the log-transformed variable used to calculate bioavailability

Depodur was 89% bioavailable compared to morphine sulfate injection and demonstrated dose proportionality over a dose range of 5 to 25mg.

**Distribution, Metabolism and Excretion of Morphine Sulfate**

After morphine sulfate has been released from Depodur and is absorbed systemically, its distribution, metabolism and excretion are the same as other morphine formulations. Depodur is intended for single dose administration; therefore accumulation of morphine or its metabolites is not expected even in patients with impaired hepatic or renal function.

5.3. Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional toxicology studies.

6. **PHARMACEUTICAL PARTICULARS**

6.1. **List of excipients**

- Dioleoylphosphatidylcholine
- Dipalmitoylphosphatidylglycerol
- Cholesterol
- Triolein
- Tricaprylin
- Sodium chloride
- Diluted (10%) hydrochloric acid
- Water for injections

6.2. Incompatibilities
Do not mix Depodur with any other medications. Once Depodur has been administered, no other medication should be administered into the epidural space for at least 48 hours.

6.3. Shelf life

2 years

From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately.

6.4. Special precautions for storage

Store in a refrigerator (2° to 8°C).
Do not freeze. Where there is evidence or suspicion that Depodur has been frozen, it should be disposed of in the way specified for opioid drugs.
Avoid aggressive shaking.

Keep the vials in the outer carton. The outer cartons contain 5 vials. A freeze indicator that is visible through the top of the carton indicates exposure to a temperature below 0°C. It is important that the freeze indicator is inspected before removal of a vial from the carton. Vials from this carton should only be used if the solution in the bulb of the freeze indicator is clear. If the solution in the bulb is coloured, then the product should be destroyed.

Depodur may be held for up to 7 days at up to 25°C in sealed, intact (unopened) vials.

6.5. Nature and contents of container

Depodur is available in 15mg/1.5ml single-use, Type I amber glass vials with ethylenetetrafluoroethylene (ETFE) stoppers and aluminium caps. Pack sizes are as follows:

15mg/1.5ml vials packaged in cartons of 5

6.6. Instructions for use and handling and disposal

Depodur consists of morphine encapsulated in multivesicular lipid-based particles that pose no known risk of handling to health care workers.

Each vial of Depodur contains a potent opioid that has been associated with abuse and dependence among health care providers. Appropriate measures should be taken to control this product within the hospital or clinic including rigid accounting, rigorous control of wastage, and restricted access.
7. MARKETING AUTHORITY HOLDING

SkyePharma PLC
105 Piccadilly
London
W1J 7NJ
UK

8. MARKETING AUTHORITY NUMBER

PL 20334/0003

9. DATE OF FIRST AUTHORITY RENEWAL OF THE AUTHORIZATION

20/04/2006

10. DATE OF REVISION OF THE TEXT

20/04/2006
1. NAME OF THE MEDICINAL PRODUCT

Depodur 20mg/2 ml Suspension for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 20mg/2 ml morphine sulfate pentahydrate.

For excipients, see Section 6.1

3. PHARMACEUTICAL FORM

Suspension for Injection

White to off-white homogeneous suspension

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

For the relief of post-operative pain for up to 48 hours.

4.2. Posology and method of administration

**Adults and the elderly**

Depodur is intended only for epidural administration. Intravenous, intramuscular and intrathecal administration are contraindicated. Depodur may be administered peri-operatively via needle or catheter at the lumbar and lower thoracic levels, except in caesarean section (see below). Administration of Depodur at the mid-thoracic level or higher has not been studies. Depodur may be administered undiluted or may be diluted up to 5ml total volume with preservative-free 0.9% normal saline.

Table 1: Dosing Recommendations by Surgery Type and Patient Age

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<th>Surgical Populations</th>
<th>Age categories</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 65 years</td>
</tr>
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MHRA PAR -Depodur Suspension for Injection PL20334/0002-4
Depodur has been administered to women undergoing caesarean section following clamping of the umbilical cord. Depodur should not be administered to women for vaginal labour and delivery.

Depodur should be administered by or under the direction of a physician experienced in the technique of epidural administration and who is thoroughly familiar with the labelling of this product.

Improper placement of a needle or catheter in the epidural space should be ruled out before Depodur is injected. Acceptable techniques to rule out improper placement of a needle or catheter include: a) aspiration to check for absence of blood or cerebrospinal fluid and/or b) administration of 3ml of 1.5% preservative-free lidocaine and adrenaline (1:200,000) test dose. If a test dose is administered, observe the patient for lack of tachycardia (this indicates that vascular injection has not occurred) and lack of segmental anaesthesia (this indicates that intrathecal administration has not occurred). To minimise a pharmacokinetic interaction of Depodur with the test dose, flush the catheter/needle with 1ml of preservative-free 0.9% normal saline and wait for at least 10 minutes after administration of the test dose before administering Depodur.

Do not mix Depodur with any other medications. Once Depodur has been administered, no other medication should be administered into the epidural space for at least 48 hours.

Do not use an in-line filter during administration of Depodur.

Depodur is a sterile agent; however, it does not contain any bacteriostatic agents. Therefore, Depodur must be administered within 4 hours after withdrawal from the vial. Do not heat-sterilise or gas-sterilise.

Discard any unused portion in a manner appropriate for controlled drugs.

Protect Depodur from freezing. Do not administer Depodur if it is suspected that the vial has been frozen.

Paediatrics
The safety and effectiveness of Depodur in paediatric patients below the age of 18 years has not yet been established.

4.3. Contraindications

Depodur is contraindicated in patients with known hypersensitivity to morphine, morphine salts, or any components of the product. Depodur, like all opioids, is contraindicated in patients with respiratory depression, acute or severe bronchial asthma, or upper airway obstruction. Any contraindications for an epidural injection
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4.4. Special warnings and precautions for use

No clinical studies have evaluated the safety of administration of Depodur into the intrathecal space. Studies in dogs administered Depodur intrathecally demonstrated no toxicity attributable to the lipid component of Depodur. While the adverse effects observed in these dogs were typical opioid side effects consistent with the dose of morphine administered, profound and prolonged respiratory depression would be expected in humans.

Prior to drug administration, the physician should be familiar with patient conditions (such as infection at the injection site, bleeding diathesis, current and anticipated anticoagulant therapy etc.) that call for special evaluation of the benefit versus risk potential.

Use with caution in opiate-dependent patients and patients with decreased pulmonary function, raised intracranial pressure, hypotension with hypovolaemia, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, prostatic hypertrophy, sleep apnoea, and adrenocortical insufficiency.

Respiratory depression is of particular concern for all epidural opioid preparations. If the surgical procedure is cancelled after the administration of Depodur, the risk of respiratory depression may be increased because of the missing pain stimulus. Because of the risk of respiratory depression, the facility must be equipped to resuscitate patients. Patients must be closely monitored in a fully equipped and staffed environment for at least 24 hours after Depodur administration with additional monitoring for an additional 24 hours, especially if the surgical procedure was after administration of Depodur.

In addition, Depodur may cause hypotension, paralytic ileus, urinary retention, biliary colic, somnolence, pruritis, nausea and vomiting.

4.5. Interactions with other medicinal products and other forms of interaction

Local anaesthetics: Clinical studies have demonstrated that administration of Depodur three minutes after a 3ml test-dose (lidocaine 1.5% and adrenaline 1:200,000) increases peak serum concentrations of morphine. However, no clinically meaningful effects on safety or efficacy were observed, despite the administration of such a test dose. Increasing the interval between the test dose and Depodur administration to at least 10 minutes minimises this pharmacokinetic interaction. Please see the dosage recommendations in Section 4.2 in respect of this interaction.

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Monoamine Oxidase Inhibitors (MAOIs): MAOIs markedly potentiate the action of morphine. Depodur should not be used in patients taking MAOIs or within 14 days of stopping such treatment.

4.6. **Pregnancy and lactation**

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Depodur, in common with other opioids, has CNS depressant effects. Effects on the ability to drive or operate machinery have not been studied, but it is expected to have a major influence on the ability to drive or operate machines within 48 hours of administration. Therefore, patients should not drive or use heavy machinery within 48 hours of administration.

4.8. **Undesirable effects**

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Overdosage of morphine is characterised by respiratory depression, with or without concomitant CNS depression. Since respiratory arrest may result either through
direct depression of the respiratory centre or as a result of hypoxia, primary attention should be given to the establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. The opioid antagonist, naloxone, is a specific antidote. An initial dose of 0.4 to 2 mg of naloxone should be administered intravenously, simultaneously with respiratory resuscitation. If the desired degree of counteraction and improvement in respiratory function is not obtained, naloxone may be repeated at 2 to 3 minute intervals. If no response is observed after 10mg of naloxone has been administered, the diagnosis of opioid-induced, or partial opioid-induced, toxicity should be questioned. Intramuscular or subcutaneous administration of naloxone may be used if the intravenous route is not available.

As the duration of effect of naloxone is considerably shorter than that of Depodur, repeated administration or continuous infusion of naloxone may be necessary. Patients should be closely observed for evidence of recurrence of respiratory depression.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloid
ATC Code: N02A 01

Morphine acts as an agonist at opiate receptors in the CNS, particularly mu and, to a lesser extent, kappa receptors. Mu receptors are thought to mediate supraspinal analgesia, respiratory depression, and euphoria, and kappa receptors, spinal analgesia, miosis, and sedation. Morphine also has a direct action on the bowel wall nerve plexuses, causing constipation.

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<th>PK Parameter</th>
<th>Depodur 5mg (n = 10)</th>
<th>Morphine sulfate Injection 5mg (N = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_{\text{max}} ) (ng/ml)</td>
<td>7.10 3.40</td>
<td>25.35 12.01</td>
</tr>
<tr>
<td>( T_{\text{max}} ) (hr)(^1)</td>
<td>1.00 (0.25 – 4.0)</td>
<td>0.25 (0.25 – 2.0)</td>
</tr>
<tr>
<td>AUC (ng.hr/ml)</td>
<td>38.80 10.35</td>
<td>44.07 7.95</td>
</tr>
<tr>
<td>( t_{1/2} ) (hr)</td>
<td>3.82 1.00</td>
<td>2.25 0.45</td>
</tr>
<tr>
<td>AUC(^2)</td>
<td>37.41</td>
<td>43.48</td>
</tr>
</tbody>
</table>

\(^1\) Median (range)
\(^2\) Geometric mean of the log-transformed variable used to calculate bioavailability

Depodur was 89% bioavailable compared to morphine sulfate injection and demonstrated dose proportionality over a dose range of 5 to 25mg.

Distribution, Metabolism and Excretion of Morphine Sulfate
After morphine sulfate has been released from Depodur and is absorbed systemically, its distribution, metabolism and excretion are the same as other morphine formulations. Depodur is intended for single dose administration; therefore accumulation of morphine or its metabolites is not expected even in patients with impaired hepatic or renal function.

5.3. Preclinical safety data
Preclinical data reveal no special hazard for humans based on conventional toxicology studies.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients
Dioleoylphosphatidylcholine
Dipalmitoylphosphatidylglycerol
Cholesterol
Triolein
Tricaprylin
Sodium chloride
Diluted (10%) hydrochloric acid
Water for injections

6.2. Incompatibilities
Do not mix Depodur with any other medications. Once Depodur has been administered, no other medication should be administered into the epidural space for at least 48 hours.

6.3. Shelf life

2 years

From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately.

6.4. Special precautions for storage

Store in a refrigerator (2° to 8°C).
Do not freeze. Where there is evidence or suspicion that Depodur has been frozen, it should be disposed of in the way specified for opioid drugs.
Avoid aggressive shaking.
Keep the vials in the outer carton.

The outer cartons contain 5 vials. A freeze indicator that is visible through the top of the carton indicates exposure to a temperature below 0°C. It is important that the freeze indicator is inspected before removal of a vial from the carton. Vials from this carton should only be used if the solution in the bulb of the freeze indicator is clear. If the solution in the bulb is coloured, then the product should be destroyed.

Depodur may be held for up to 7 days at up to 25°C in sealed, intact (unopened) vials.

6.5. Nature and contents of container

Depodur is available in 20mg/2 ml single-use, Type I amber glass vials with ethylenetetrafluoroethylene (ETFE) stoppers and aluminium caps. Pack sizes are as follows:

20mg/2ml vials packaged in cartons of 5

6.6. Instruction for use and handling and disposal

Depodur consists of morphine encapsulated in multivesicular lipid-based particles that pose no known risk of handling to health care workers.

Each vial of Depodur contains a potent opioid that has been associated with abuse and dependence among health care providers. Appropriate measures should be taken to control this product within the hospital or clinic including rigid accounting, rigorous control of wastage, and restricted access.
6.6. Instructions for use and handling and disposal

Depodur consists of morphine encapsulated in multivesicular lipid-based particles that pose no known risk of handling to health care workers.

Each vial of Depodur contains a potent opioid that has been associated with abuse and dependence among health care providers. Appropriate measures should be taken to control this product within the hospital or clinic including rigid accounting, rigorous control of wastage, and restricted access.

7. MARKETING AUTHORISATION HOLDER

SkyePharma PLC
105 Piccadilly
London
W1J 7NJ
UK

8. MARKETING AUTHORISATION NUMBER

PL 20334/0004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/04/2006

10. DATE OF REVISION OF THE TEXT

20/04/2006
DEPODUR 10MG/1ML SUSPENSION FOR INJECTION
PL20334/0002

PATIENT INFORMATION LEAFLET

Depodur™ 10 mg/ 1 ml Suspension for Injection (morphine sulfate pentahydrate)

PATIENT INFORMATION LEAFLET

READ ALL OF THIS LEAFLET CAREFULLY BEFORE YOU RECEIVE THIS MEDICINE.

Keep this leaflet. You may need to read it again. If you have further questions, please ask your doctor or your medical staff looking after you.

IN THIS LEAFLET:

1. What Depodur is and what it is given for
2. Before you are given Depodur
3. How is Depodur given?
4. Possible side effects
5. Storing Depodur
6. Further information

DEPODUR 10 MG/ 1 ML SUSPENSION FOR INJECTION (MORPHINE SULFATE PENTAHYDRATE)

The active substance is morphine sulfate pentahydrate. The concentration of morphine sulfate pentahydrate in Depodur is 10 mg/ml. Each vial of 1 ml contains 10 mg morphine sulfate pentahydrate (10 mg/ml). Depodur is supplied in cartons containing 5 vials.

The product also contains: triolein, tricaprylin, cleyethylphosphatidylcholine, dipalmitoylphosphatidylglycerol, sodium chloride, diol (10%), hydrochloric acid, and water for injections.

Depodur contains less than 1 mmol sodium (23 mg) per 10 ml, i.e., it is essentially "sodium-free".

The marketing authorisation holder is SkyePharma PLC, 105 Piccadilly, London, W1J 7NJ, United Kingdom.

The manufacturer is PDMS, Almec House, 20 Seagoe Industrial Estate, Craigavon, Co. Armagh, Northern Ireland, BT63 5QO.

1. WHAT DEPODUR IS AND WHAT IT IS GIVEN FOR

Each vial contains 1 ml of suspension for a single injection. Each ml of product contains 10 mg morphine sulfate pentahydrate. Morphine sulfate pentahydrate is a natural opium alkaloid.

Depodur is used to provide pain relief immediately following a surgical operation. It is injected into the epidural space in the spine. The morphine sulfate in Depodur will be released over time to provide pain relief for up to 48 hours, decreasing the need for other pain medication.

2. BEFORE YOU ARE GIVEN DEPODUR

You should not be given Depodur:

- if you are allergic to morphine or any of the other ingredients in Depodur
- if you are receiving epidural anaesthesia
- if you have severe problems with your breathing
- if you have medical condition that makes an epidural injection unsafe, such as a blood infection or abnormal blood clotting
- if you have an acute, severe abdominal condition called paralytic ileus

Depodur is not recommended for patients under 18 years of age.

Monitoring requirements: Depodur can occasionally cause breathing to become too slow, which can be delayed, profound and of sudden onset. Because this could be dangerous if unrecoined and untreated, continuous monitoring and observation for 48 hours following administration of Depodur is mandatory.

Pregnancy: Depodur can be given to women undergoing caesarean section after the umbilical cord has been clamped, where adequate monitoring facilities are available. Depodur should not be given to women for vaginal labour and delivery, or to women who have received epidural local anaesthetics for pain relief during labour.

Breast-feeding: Small amounts of morphine sulfate may pass into breast milk after administration of any morphine formulation. If you are breast-feeding ask your doctor or anaesthetist for advice before being given Depodur.

Driving and using machines: Depodur is given prior to or during a surgical operation and typically stays in your body for approximately 48 hours. Therefore, you should not drive or operate heavy equipment for at least 48 hours after receiving Depodur.

MHRA PAR -Depodur Suspension for Injection PL20334/0002-4 - 106 -
IF YOU ARE TAKING OR USING OTHER MEDICINES:

Make sure the anaesthetist is aware if you are taking sedative or tranquilliser medicines, other strong pain killers or any medicines that may cause sedation as a side effect, or if you have recently drunk alcohol, as they may react badly with Depodur.

You should not receive Depodur if you are taking a class of medicines called monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping treatment with MAOIs.

Please inform your doctor or physician if you are taking or using any of these or other medicines, even those not prescribed.

3. HOW IS DEPODUR GIVEN?

An anaesthetist will inject Depodur in the space around the spinal cord. Depodur must not be given any other way.

The anaesthetist may give a local anaesthetic/adrenaline (epinephrine) test dose in order to rule out accidental placement of the needle or catheter into a vein or too deep in the spine. In these cases, Depodur must be given after flushing the catheter with saline and waiting for at least 10 minutes.

Depodur may be used as supplied, but also can be diluted up to 5-nil total volume with preservative-free 0.9% normal saline.

Depodur should not be filtered before it is given.

The dose depends on the type of surgery. The following doses are usual:

- 15 mg for hip and knee surgeries
- 10 – 15 mg for lower abdominal or pelvic surgeries
- 15 mg for caesarean sections

The maximum recommended dose in adults up to 65 years is 20 mg. The maximum recommended dose in elderly (≥ 65 years) or frail patients is 15 mg.

If you are given more Depodur than you should receive, there is an antidote. A type of drug called an opioid antagonist can be given to prevent the effects of the morphine sulfate in Depodur. This may also reverse some of the pain killer effect.

4. POSSIBLE SIDE EFFECTS

As with all medicines, Depodur may also cause side effects.

Depodur like all other morphine preparations, can sometimes cause you to feel sick (or even vomit). After receiving Depodur you may experience skin itching, skin redness and inflammation, fever, headache, constipation, dizziness, flattulence, rapid heart beat and difficulty sleeping. You may experience decreased sensitivity to stimulation from things such as light, touch or pain, or encounter abnormal sensations such as numbness, tingling or burning. You are likely to have difficulty passing urine from the bladder. Importantly, you may develop poor or difficulty breathing, weakness, slowed heart beat and dizziness when you stand up. You may be difficult to awaken, have dulled senses, feel more confused or less alert than usual or you may become unconscious.

If you notice any side effects either listed or not listed in this leaflet, please notify a member of the staff taking care of you.

5. STORING DEPODUR

Keep out of reach and sight of children.

Store in a refrigerator (2°C to 8°C). Do not freeze. Avoid aggressive shaking.

Keep the vials in the outer carton. The outer cartons contain 5 vials. A freeze indicator that is visible through the top of the carton indicates exposure to a temperature below 0°C. It is important that the freeze indicator is inspected before removal of a vial from the carton. Vials from this carton should only be used if the solution in the bulb of the freeze indicator is clear. If the solution in the bulb is coloured, then the product should be destroyed.

Depodur may be held for up to 7 days at up to 25°C in sealed, intact (unopened) vials.

Do not use after the expiry date stated on the vial.

Vials of Depodur should be gently inverted to re-suspend the particles immediately prior to withdrawal from the vial.

Any unused portion in the vial should be discarded.

This leaflet was last updated in (date).

6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

Zeneus Pharma Ltd.
Abel Smith House
Gunnels Wood Road
Stevenage, Herts
SG1 2BT, UK
Tel: +44 (0) 1438 765100
PATIENT INFORMATION LEAFLET

Depodur™ 15 mg/1.5 ml Suspension for Injection (morphine sulfate pentahydrate)

READ ALL OF THIS LEAFLET CAREFULLY BEFORE YOU RECEIVED THIS MEDICINE.

Keep this leaflet. You may need to read it again. If you have further questions, please ask your doctor or your medical staff looking after you.

IN THIS LEAFLET:
1. What Depodur is and what it is used for
2. Before you are given Depodur
3. How is Depodur given?
4. Possible side effects
5. Storing Depodur
6. Further information

DEPODUR 15 MG/1.5 ML SUSPENSION FOR INJECTION (MORPHINE SULFATE PENTAHYDRATE)

The active substance is morphine sulfate pentahydrate. The concentration of morphine sulfate pentahydrate in Depodur is 15 mg/1.5 ml. Each vial of 1.5 ml contains 15 mg morphine sulfate pentahydrate (10 mg/ml). Depodur is supplied in cartons containing 5 vials.

The product also contains: cholesterol, triolein, tricaprylin, dicetylphosphate, dimethylphosphate, glycerol, sodium chloride, diluted (10%) hydrochloric acid, and water for injections.

Depodur contains less than 1 mmol sodium (23 mg) per 10 ml, i.e., it is essentially “sodium-free”.

The marketing authorisation holder is: Skyepharma PLC, 105 Piccadilly, London, W1J 7NJ, United Kingdom.

The manufacturer is: PDM5, Almac House, 20 Seagoe Industrial Estate, Craigavon, Co. Armagh, Northern Ireland, BT63 5QD.

1. WHAT DEPODUR IS AND WHAT IT IS USED FOR

Each vial contains 1.5 ml of suspension for a single injection. Each ml of product contains 10 mg morphine sulfate pentahydrate. Morphine sulfate pentahydrate is a natural opium alkaloid.

Depodur is used to provide pain relief immediately following a surgical operation. It is injected into the epidural space in the spine. The morphine sulfate in Depodur will be released over time to provide pain relief for up to 48 hours, decreasing the need for other pain medication.

2. BEFORE YOU ARE GIVEN DEPODUR

You should not be given Depodur:

- If you are allergic to morphine or any of the other ingredients in Depodur
- If you are receiving epidural anaesthesia
- If you have severe problems with your breathing
- If you have medical condition that makes an epidural injection unsafe, such as a blood infection or abnormal blood clotting
- If you have an acute, severe abdominal condition called paralytic ileus

Depodur is not recommended for patients under 18 years of age.

Monitoring requirements: Depodur can occasionally cause breathing to become too slow, which can be delayed, profound and of sudden onset. Because this could be dangerous if unrecognised and untreated, continuous monitoring and observation for 48 hours following administration of Depodur is mandatory.

Pregnancy: Depodur can be given to women undergoing caesarean section after the umbilical cord has been clamped, where adequate monitoring facilities are available. Depodur should not be given to women for vaginal labour and delivery, or to women who have received epidural local anaesthetics for pain relief during labour.

Breast-feeding: Small amounts of morphine sulfate may pass into breast milk after administration of any morphine formulation. If you are breast-feeding ask your doctor or anaesthetist for advice before being given Depodur.

Driving and using machines: Depodur is given prior to or during a surgical operation and typically stays in your body for approximately 48 hours. Therefore, you should not drive or operate heavy equipment for at least 48 hours after receiving Depodur.
IF YOU ARE TAKING OR USING OTHER MEDICINES:

Make sure the anaesthetist is aware if you are taking sedative or tranquiliser medicines, other strong pain killers or any medicines that may cause sedation as a side effect, or if you have recently drunk alcohol, as they may react badly with Depodur.

You should not receive Depodur if you are taking a class of medicines called monamine oxidase inhibitors (MAOIs) or within 14 days of stopping treatment with MAOIs.

Please inform your doctor or physician if you are taking or using any of these or other medicines, even those not prescribed.

3. HOW IS DEPODUR GIVEN?

An anaesthetist will inject Depodur in the space around the spinal cord. Depodur must not be given any other way.

The anaesthetist may give a local anaesthetic/adrenaline (epinephrine) test dose in order to rule out accidental placement of the needle or catheter into a vein or too deep in the spine. In these cases, Depodur must be given after flushing the catheter with saline and waiting for at least 10 minutes.

Depodur may be used as supplied, but also can be diluted up to 5-ml total volume with preservative-free 0.9% normal saline.

Depodur should not be filtered before it is given.

The dose depends on the type of surgery. The following doses are usual:

- 15 mg for hip and knee surgeries
- 10 – 15 mg for lower abdominal or pelvic surgeries
- 10 mg for caesarean sections

The maximum recommended dose in adults up to 65 years is 20 mg. The maximum recommended dose in elderly (≥ 65 years) or frail patients is 15 mg.

If you are given more Depodur than you should receive, there is an antidote. A type of drug called an opioid antagonist can be given to prevent the effects of the morphine sulfate in Depodur. This may also reverse some of the pain killer effect.

4. POSSIBLE SIDE EFFECTS

As with all medicines, Depodur may also cause side effects.

Depodur like all other morphine preparations, can sometimes cause you to feel sick (or even vomit). After receiving Depodur you may experience skin itching, skin redness and inflammation, fever, headache, constipation, dizziness, flatulence, rapid heart beat and difficulty sleeping. You may experience decreased sensitivity to stimulation from things such as light, touch or pain, or encounter abnormal sensations such as numbness, tingling or burning. You are likely to have difficulty passing urine from the bladder. Importantly, you may develop poorer or difficulty breathing, weakness, slowed heart beat and dizziness when you stand up. You may be difficult to awaken, have dulled senses, feel more confused or less alert than usual or you may become unconscious.

If you notice any side effects either listed or not listed in this leaflet, please notify a member of the staff taking care of you.

5. STORING DEPODUR

Keep out of reach and sight of children.

Store in a refrigerator (2°C to 8°C).

Do not freeze.

Avoid aggressive shaking.

Keep the vials in the outer carton. The outer cartons contain 5 vials. A freeze indicator that is visible through the top of the carton indicates exposure to a temperature below 0°C. It is important that the freeze indicator is inspected before removal of a vial from the carton. Vials from this carton should only be used if the solution in the bulb of the freeze indicator is clear. If the solution in the bulb is coloured, then the product should be destroyed.

Depodur may be held for up to 7 days at up to 25°C in sealed, intact (unopened) vials.

Do not use after the expiry date stated on the vial.

Vials of Depodur should be gently inverted to re-suspend the particles immediately prior to withdrawal from the vial.

Any unused portion in the vial should be discarded.

This leaflet was last updated in (date).

6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

Zeneus Pharma Ltd.
Abel Smith House
Gunndals Wood Road
Stevenage, Herts
SG1 2BT, UK
Tel: +44 (0) 1438 765100
Depodur™ 20 mg/2 ml Suspension for Injection (morphine sulfate pentahydrate)

PATIENT INFORMATION LEAFLET

READ ALL OF THIS LEAFLET CAREFULLY BEFORE YOU RECEIVE THIS MEDICINE.

Keep this leaflet. You may need to read it again. If you have further questions, please ask your doctor or your medical staff looking after you.

IN THIS LEAFLET:

1. What Depodur is and what it is given for
2. Before you are given Depodur
3. How is Depodur given?
4. Possible side effects
5. Storing Depodur
6. Further information

DEPODUR 20 MG/2 ML SUSPENSION FOR INJECTION (MORPHINE SULFATE PENTAHYDRATE)

The active substance is morphine sulfate pentahydrate. The concentration of morphine sulfate pentahydrate in Depodur is 20 mg/2 ml. Each vial of 2 ml contains 20 mg morphine sulfate pentahydrate (10 mg/ml). Depodur is supplied in cartons containing 5 vials.

The product also contains cholesterol, triolein, tricaprylin, dioleoylphosphatidylcholine, dipalmitoylphosphatidylglycerol, sodium chloride, diluted (10%) hydrochloric acid, and water for injections.

Depodur contains less than 1 mmol sodium (23 mg) per 10 ml, i.e., it is essentially “sodium-free”.

The marketing authorisation holder is Skypharma PLC, 105 Piccadilly, London, W1J 7NJ, United Kingdom.

The manufacturer is PDMS, Almac House, 20 Seagoe Industrial Estate, Craigavon, Co. Armagh, Northern Ireland, BT63 5QD.

1. WHAT DEPODUR IS AND WHAT IT IS GIVEN FOR

Each vial contains 2 ml of suspension for a single injection.

Each ml of product contains 10 mg morphine sulfate pentahydrate.

Morphine sulfate pentahydrate is a natural opium alkaloid.

Depodur is used to provide pain relief immediately following a surgical operation. It is injected into the epidural space in the spine. The morphine sulfate in Depodur will be released over time to provide pain relief for up to 48 hours, decreasing the need for other pain medication.

2. BEFORE YOU ARE GIVEN DEPODUR

You should not be given Depodur:

- If you are allergic to morphine or any of the other ingredients in Depodur
- If you are receiving epidural anaesthesia
- If you have severe problems with your breathing
- If you have medical condition that makes an epidural injection unsafe, such as a blood infection or abnormal blood clotting
- If you have an acute, severe abdominal condition called paralytic ileus

Depodur is not recommended for patients under 18 years of age.

Monitoring requirements: Depodur can occasionally cause breathing to be too slow, which can be delayed, profound and of sudden onset. Because this could be dangerous if unrecognised and untreated, continuous monitoring and observation for 48 hours following administration of Depodur is mandatory.

Pregnancy: Depodur can be given to women undergoing caesarean section after the umbilical cord has been clamped, where adequate monitoring facilities are available. Depodur should not be given to women for vaginal labour and delivery, or to women who have received epidural local anaesthetics for pain relief during labour.

Breast-feeding: Small amounts of morphine sulfate may pass into breast milk after administration of any morphine formulation. If you are breastfeeding ask your doctor or anaesthetist for advice before being given Depodur.

Driving and using machines: Depodur is given prior to or during a surgical operation and typically stays in your body for approximately 48 hours. Therefore, you should not drive or operate heavy equipment for at least 48 hours after receiving Depodur.
IF YOU ARE TAKING OR USING OTHER MEDICINES:

Make sure the anaesthetist is aware if you are taking sedative or tranquiliser medicines, other strong pain killers or any medicines that may cause sedation as a side effect, or if you have recently drunk alcohol, as they may react badly with Depodur.

You should not receive Depodur if you are taking a class of medicines called monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping treatment with MAOIs.

Please inform your doctor or physician if you are taking or using any of these or other medicines, even those not prescribed.

3. HOW IS DEPODUR GIVEN?

An anaesthetist will inject Depodur in the space around the spinal cord. Depodur must not be given any other way.

The anaesthetist may give a local anaesthetic/adrenaline (epinephrine) test dose in order to rule out accidental placement of the needle or catheter into a vein or too deep in the spine. In these cases, Depodur must be given after flushing the catheter with saline and waiting for at least 10 minutes.

Depodur may be used as supplied, but also can be diluted up to 5ml total volume with preservative-free 0.9% normal saline.

Depodur should not be filtered before it is given.

The dose depends on the type of surgery. The following doses are usual:

- 15 mg for hip and knee surgeries
- 10 – 15 mg for lower abdominal or pelvic surgeries
- 10 mg for caesarean sections

The maximum recommended dose in adults up to 65 years is 20 mg. The maximum recommended dose in elderly (< 65 years) or frail patients is 15 mg.

If you are given more Depodur than you should receive, there is an antidote. A type of drug called an opioid antagonist can be given to prevent the effects of the morphine sulfate in Depodur. This may also reverse some of the pain killer effect.

4. POSSIBLE SIDE EFFECTS

As with all medicines, Depodur may also cause side effects.

Depodur like all other morphine preparations, can sometimes cause you to feel sick (or even vomit). After receiving Depodur you may experience skin itching, skin redness and inflammation, fever, headache, constipation, dizziness, flatulence, rapid heart beat and difficulty sleeping. You may experience decreased sensitivity to stimulation from things such as light, touch or pain, or encounter abnormal sensations such as numbness, tingling or burning. You are likely to have difficulty passing urine from the bladder. Importantly, you may develop poor or difficulty breathing, weakness, slowed heart beat and dizziness when you stand up. You may be difficult to awaken, have dulled senses, feel more confused or less alert than usual or you may become unconscious.

If you notice any side effects either listed or not listed in this leaflet, please notify a member of the staff taking care of you.

5. STORING DEPODUR

Keep out of reach and sight of children.

Store in a refrigerator (2°C to 8°C). Do not freeze.

Avoid aggressive shaking.

Keep the vials in the outer carton. The outer cartons contain 5 vials. A freeze indicator that is visible through the top of the carton indicates exposure to a temperature below 0°C. It is important that the freeze indicator is inspected before removal of a vial from the carton. Vials from this carton should only be used if the solution in the bulb of the freeze indicator is clear. If the solution in the bulb is coloured, then the product should be destroyed.

Depodur may be held for up to 7 days at up to 25°C in sealed, intact (unopened) vials.

Do not use after the expiry date stated on the vial.

Vials of Depodur should be gently inverted to re-suspend the particles immediately prior to withdrawal from the vial.

Any unused portion in the vial should be discarded.

This leaflet was last updated in (date).

6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

Zeneca Pharma Ltd.
Abal Smith House
Gunnels Wood Road
Stovorano, Herts
SG1 2BT, UK
Tel: +44 (0) 1438 765100
DEPODUR 10MG/1ML SUSPENSION FOR INJECTION

PL20334/0002

LABELLING

VIAL
DEPODUR 15MG/1.5ML SUSPENSION FOR INJECTION

PL20334/0003

LABELLING

VIAL

For epidural use only
Each vial contains 1.5 ml suspension
Marketing Authorisation Holder: SkyePharma PLC
Distributed by: Zeneus Pharma Limited

Lot EXP
DEPODUR 20MG/2ML SUSPENSION FOR INJECTION

PL20334/0004

LABELLING

VIAL