PRE-CLINICAL AND CLINICAL EXPERT REPORT

1. INTRODUCTION

The Dioctyl range of products has been marketed for at least 20 years. It includes Dioctyl Tablets containing 100 mg docusate sodium, Dioctyl Syrup containing docusate sodium 1% w/v and Dioctyl Paediatric Syrup containing docusate sodium 0.25% w/v. The products are indicated for the prevention and treatment of chronic constipation, although they are also used for bowel clearance prior to radiological procedures.

A review of standard reference works and other published literature is presented in support of the well known efficacy and tolerability of docusate sodium.

2. PRE-CLINICAL DATA

Docusate sodium is a well-known substance which has been in widespread use for very many years. Consequently, pharmacological and toxicological information has not been included in this application.

3. CLINICAL EVIDENCE

3.1 SUMMARY OF PRODUCT CHARACTERISTICS

The following is a summary of proposed particulars:

3.1.1 Active constituents

Dioctyl Tablets:	100 mg docusate sodium
Dioctyl Syrup:	1% w/v docusate sodium (50 mg in 5 ml)
Dioctyl Paediatric Syrup:	0.25% w/v docusate sodium (12.5 mg in 5 ml)

3.1.2 Uses

Docusate sodium is an anionic wetting agent which acts as a faecal softener by allowing penetration of accumulated, hard, dry faeces by water and fats. Used for the prevention and treatment of chronic constipation.

3.1.3 Dosage and administration

For constipation

Adults: Up to 500 mg in divided doses daily. Treatment should be commenced with large doses which should be decreased as the patient improves.

Children: 12.5 to 25 mg three times daily

Infants over six months: 12.5 mg three times daily

For barium meals: 400 mg to be taken with the meal.

3.1.4 Contraindications, warnings etc.

Anthraquinone derivatives should be taken in a reduced dose when administered with docusate sodium as it increases their absorption. Do not use when abdominal pain, nausea or vomiting is present. Do not take concurrently with mineral oil. Not to be given to infants under six months.

3.1.5 Pharmacological particulars

Docusate sodium acts as a faecal softener by increasing the penetration of water and fats.

3.2 EFFICACY

3.2.1 Mode of Action

The mode of action of docusate sodium is postulated to be two-fold. Firstly, the material is an anionic surfactant with wetting, dispersing, detergent and emulsifying actions (1). In vivo this allows water to penetrate faecal masses, softening them and increasing bulk.

A stimulant laxative has been defined as any drug which may affect intestinal salt and water fluxes or may stimulate peristalsis (5). Docusate sodium has been shown to inhibit water absorption in both rats and humans and to alter the histological appearance of cells of rat colon and is therefore described in several texts as a stimulant laxative (2,5,6). It has also been suggested that the increased bulk of faeces, caused by absorption of water may help to stimulate peristalsis (3).

3.2.2 Clinical evidence

The use of docusate sodium as a stool softener is well documented in standard reference works [1,2,3,4,6,7]. In addition, the substance is currently available in the United Kingdom as an ingredient of other laxative products such as Normax (in which it is combined with danthron) and Fletcher's Enemette (an enema preparation of docusate alone, manufactured by Pharmax). Both these products hold full product licences. However, due to long-established use of the substance there is very little evidence available from formal clinical trials to support the efficacy of the product in clinical use. In particular, there is a lack of data on Medo Pharmaceutical's docusate preparations.

In 1968 Hyland [8] investigated the effect of docusate sodium (100 mg docusate sodium, previously named Dioctyl Medo Forte) in a double-blind placebo controlled cross-over study in 40 geriatric patients. Patients received 100 mg of Dioctyl Forte given three times daily over a four week period. Docusate sodium was found to be significantly more effective than placebo in terms of increased number of stools per week and overall subjective impressions. However, the study was not well reported by present-day standards. In particular, some patients in the placebo group were excluded from the efficacy analysis due to their chronic constipation being absent during placebo treatment.

Fain et al [11] in 1978 performed a better-designed study of docusate sodium 100-200 mg, compared with docusate calcium and placebo. This study showed that docusate sodium produced no significant benefit over placebo.

The efficacy of docusate sodium has also been investigated in a double-blind comparative study between Normax (danthron and docusate sodium), senna and bulk-forming laxatives in antenatal and postnatal patients [9]. This study appeared to show no significant differences between the safety and efficacy of Normax and bulk-forming laxatives - Normacol Special and Normacol Standard (sterculia and sterculia/frangula combination respectively).

However, there was a trend which indicated that in postnatal women Normax and senna, might have been more efficacious than the bulk-forming laxatives, but associated with more adverse effects, such as abdominal pain and diarrhoea.

Finally, an open label study [10] in post-operative patients showed that a combination of senna and docusate sodium gave good results in terms of safety and efficacy.

3.2.3 Dosage and Administration

The recommended dosages of docusate sodium, listed in standard reference works are as follows:

Martindale[1]:

Adults	-	50-300 mg/day in divided doses. 500 mg has been used.
Children	-	5 mg/kg daily in divided doses.
Rectally	-	use a 0.1% solution.

British National Formulary[5]:

Orally	-	Adults: up to 500 mg daily in divided doses; initial doses should be large and gradually reduced.
		Children: 12.5 to 25 mg 3 times daily. With barium meal - 400 mg.
Rectally	-	Adults: use Dioctyl Paediatric Syrup 15-40 ml.
		Children: up to 1 yr: 5-10 ml Dioctyl Paediatric Syrup.
		Children: over 1 yr: 7.5-15 ml Dioctyl Paediatric Syrup.
	or	use Dioctyl Syrup, as above, diluted with 3 parts water.

Medo's dosage recommendations correspond well, with the exception that the use of the syrup as an enema is not recommended by the manufacturer.

3.2.4 Tablet vs. Syrup Presentation

No evidence is available to compare the availability or efficacy of docusate sodium when presented in a syrup as opposed to a tablet formulation. However, extensive literature searches have been performed which have failed to reveal any evidence that efficacy of the syrup differs from that of the tablets. Since efficacy depends upon a physical effect and not upon absorption, it is believed that the two presentations can be considered to have essentially equivalent effects in vivo.

3.2.5 Comment

The Dioctyl range of products all contain docusate sodium which is a well-known substance and has been widely used for the treatment of constipation for many years. Its effectiveness in softening stools depends upon its surfactant properties. Despite a relative lack of formal clinical evidence, docusate sodium is referred to in many accepted, standard reference works. Medo Pharmaceutical's recommended indications and dosages correspond satisfactorily with those quoted in the above sources.

3.3 SAFETY

The dosages of docusate sodium recommended by Medo are within well-accepted limits (see Section 3.2.3), however a number of precautions and warnings need to be taken into account in the use of the product. Many of these cautions apply to the use of laxative drugs in general, however some are specific to surfactants, and docusate in particular.

3.3.1 Absorption and Possible Hepatic Toxicity

Originally, docusate sodium was believed to be non-absorbable, however Dujovne and Shoeman[12], in 1972 showed that patients given 100 mg or 200 mg of docusate sodium, excreted significant amounts in bile. At the time concern had arisen that combinations of docusate with oxyphenisatin (a drug which is no longer available) had produced hepatic toxicity in some patients. Dujovne also investigated the cytotoxic effects of docusate and oxyphenisatin on human liver cell cultures. They discovered that docusate,

either alone or in combination was cytotoxic, although the combination showed a greater effect.

The workers also postulated that docusate might either be increasing tissue levels of oxyphenisatin, thus potentiating the cytotoxic effect of the latter, or alternatively, that the two drugs together might be potentiating each other's cytotoxic effects by some unknown mechanism.

In the event, oxyphenisatin was later implicated in vivo as the agent responsible for causing hepatotoxicity and the substance was withdrawn. However, since then several investigators have shown that docusate sodium is capable of increasing the initial rate, but not the extent of absorption of certain other agents administered concurrently [13,14,15,16,17,18], including phenosulphonphthalein, sulfisoxazole, sulfadiazine and danthron. This is not surprising considering that docusate dosium is a surfactant. It is believed that docusate may be absorbed from an oral dose, this crossing the gastrointestinal membrane causing a transient alteration in permeability.

In summary it appears that docusate may cause an increase in the absorption of certain compounds administered concurrently and there is also evidence that it is absorbed and is cytotoxic to hepatic cells in vitro. Dobbs et al [19], produced evidence that docusate had greater intrinsic toxicity than either oxyphenisatin or danthron. Tolman [20], showed that the hepatotoxicity of danthron was increased by docusate.

None of the studies described above provided any definitive evidence to clarify the safety of docusate sodium in humans and despite the possible concerns, the drug has remained in wide use up to the present day.

The precise significance of these results in humans, when used according to the recommendations, can, however, be clarified to some extent by an examination of the safety of the product in normal use, as described in the published literature.

3.3.2 Evidence from Published Literature

Extensive literature searches have failed to reveal reports of significant adverse effects occurring with the use of docusate sodium.

One woman who suffered from delusions developed duodenal adenocarcinoma following the consumption of a bowl of soapy water every night for 20 years. She had also been taking neuroleptic agents for about 15 years[21]. It was postulated that her carcinoma might have resulted from a carcinogenic effect of detergent compounds. The authors further proposed that if this was a general property of detergents, then docusate sodium might also exert similar effects. However, the evidence for a causal link in this case is weak.

In clinical trials described in Section 3.2.2 only a low incidence of adverse reactions was observed following administration of a combination of docusate with senna to antenatal and postpartum patients[9]. No adverse reactions at all were observed in a study of docusate vs. placebo in elderly patients, however this study was not particularly well reported[8].

In common with all laxatives, docusate sodium should not be administered to patients suffering from undiagnosed abdominal pain, nausea and vomiting or intestinal obstruction[1]. Mortality is increased if given inadvertently in cases of appendicitis, for example[2]. Use of docusate sodium in these situations is contraindicated in the data sheet.

With regard to the possible enhancement of absorption of other laxative products by docusate, Medo have quite rightly recommended reduction of the dose of anthraquinone derivatives (e.g. senna bisocodyl) when administered concurrently with Dioctyl.

In addition, absorption of liquid paraffin is known to be increased by docusate and concurrent use is contra-indicated[1].

In common with all laxatives, inappropriate or excessive use of docusate can produce adverse effects, including spastic colitis and abnormalities resulting from excessive loss of water and electrolytes. For example, secondary aldosteronism, hypoalbuminaemia and excess

calcium excretion with osteomalacia. They may also result in steatorrhoea and protein-losing enteropathy[2]. When taken in accordance with the manufacturer's recommendations, however, there is no evidence that these severe syndromes are likely to occur. The exception to this is in infants, who are particularly sensitive to alterations of water and electrolyte balance[15]. For this reason Dioctyl is not recommended for infants under the age of six months.

3.3.3 Use in the elderly

The study performed by Hyland[8], discussed previously, was carried out exclusively in elderly patients, who appeared to receive satisfactory benefit from Dioctyl without adverse effects.

No more recent clinical studies have been performed to assess the safety of Dioctyl in the elderly, but there is no evidence to suggest that this might differ from younger patients.

A suitable statement to this effect has been included on the data sheet.

3.3.4 Use in Pregnancy and lactation

The current data sheet does not contain a statement concerning the use of Dioctyl in pregnancy. Only very limited data have been identified on the use of the product in pregnancy[9,22].

A suitable statement has been prepared in accordance with guidelines issued by the Committee on Review of Medicines, i.e.:

There is inadequate evidence of safety of the drug in human pregnancy, nor is there evidence from animal work that it is free from hazard, but it has been in wide use for many years without apparent ill consequence. Use in pregnancy only if the benefits outweigh the potential risks.

Docusate sodium is excreted in breast-milk and should therefore be used with caution in lactating mothers. A suitable statement has been given on the data sheet.

3.3.5 Adverse Reactions Reported to the Company

Records of complaints made by customers concerning Dioctyl products, have been maintained since 1981.

A number of these complaints concern manufacturing aspects of the products, including reports of gelatinous precipitates in the syrup presentations, or chipping or mottling of the tablet coatings. On one occasion the 1% syrup contained a dead fly. No reports of medical adverse events have ever been received concerning Dioctyl tablets.

With respect to the syrup formulation one undocumented case of suspected "allergy" to the syrup was reported. In addition 15 written complaints, together with a number of telephone enquiries (estimated as approximately 25 for the period August 1986-1988) have been received concerning an unpleasant taste or "burning sensation" produced by the product. Such complaints are probably inevitable considering that docusate has a strong and unpleasant taste which in Dioctyl Syrup has previously been masked by a strong peppermint flavour. This flavour has now been improved although it is still likely that the taste will remain unacceptable to some patients. None of the above complaints gives rise to any serious concern regarding the safety of Dioctyl. In fact these records comprise an extremely good record of safety of the products in clinical use when one considers the quantities sold. Since 1985 these have amounted to approximately 30,000 litres of paediatric syrup, 55,000 litres of adult syrup and 30 million tablets.

3.3.6 Overall comment

There is evidence to show that docusate sodium is itself absorbed and is capable of enhancing absorption of certain compounds administered concomitantly. There is also in vitro evidence that it causes hepatic cytotoxicity, although this effect has not been supported by in vivo evidence from long-term use.

When used in accordance with the manufacturer's recommendations and warnings Dioctyl would not be expected to produce any signficant adverse effects. This is confirmed by the low incidence of adverse events reported either in the published literature or to the company itself.

4. CONCLUSIONS

Dioctyl Tablets, Dioctyl Syrup and Dioctyl Paediatric Syrup have been marketed by Medo Pharmaceuticals Ltd. for at least 20 years. The active ingredient, docusate sodium, is a well-established substance having been used in indications similar to those proposed for Dioctyl for very many years.

The recommended dosages, uses and precautions etc. of Dioctyl are well in accordance with those described in published literature and standard reference works, although there is very little evidence from formal clinical trials to substantiate conclusively the drug's efficacy.

Despite some evidence that docusate may produce hepatotoxic effects, these concerns have not been supported in practice, since widespread use over many years has failed to reveal any clinically significant adverse effects. Medo Pharmaceuticals Ltd. have given appropriate contra-indications, precautions and warnings etc. on the data sheet so as to avoid inappropriate use with agents whose toxicity might be enhanced as a result of increased absorption.

In summary Dioctyl products have proved a safe and popular remedy for a common complaint for very many years. The syrups have also been used successfully prior to radiological procedures. They are considered to be suitable for retention in the U.K. marketplace.

5. REFERENCES

1. Martindale. The Extra Pharmacopoeia, 28th Edition. Ed. J.E.F. Reynolds. London. The Pharmaceutical Press. 1982.

2. The Pharmacological Basis of Therapeutics. Goodman and Gilman. Seventh Edition. MacMillan Publishing Company. New York. 1985.

3. The Merck Manual. 14th. Ed. Merck Sharp and Dohme Ltd. Herts. 1982.

4. The British Pharmacopoeia 1988. London. Her Majesty's Stationery Office.

5. SAUDERS D.R., SILLERY J. RACHMILFWITZ D. Effect of Dioctyl Sodium Sulfosuccinate on Structure and function of Rodent and Human Intestine. Gastroenterology 1975; 69: 380-386.