

**BETAMETHASONE** (Commentary)**Steroid choice**

**Are we using the ideal product?** All the glucocorticoid hormones capable of crossing the placenta (both natural and artificial) seem able to trigger the maturational process that leads to the production and release of surfactant into the alveoli of the fetal lung. However, when the New Zealand Obstetrician, Graham Liggins, discovered this property while studying the factors controlling the onset of labour in sheep in 1969, he chose to use betamethasone for his clinical trial – a product that crosses the placenta much more readily than cortisol, prednisone or prednisolone – in order to maximise the effect on the fetus while minimising maternal exposure. In addition he chose to use a commercial mixture containing equal quantities of betamethasone phosphate (which has a short half life) and betamethasone acetate (which has a relatively long half life). Glaxo originally provided such a formulation for the trial, and Schering currently market a similar product under the trade names Celestone Soluspan<sup>®</sup> and Celestone Chronodose<sup>®</sup>. Liggins hoped, by doing this, to maximise the drug's efficacy while giving the mother only one injection a day – a subtlety of design now widely overlooked. Recent research suggests that Liggins was right. The product he chose does indeed mature the lung of the fetal sheep rather better than a product that only contains betamethasone phosphate (Jobe *et al.*, 2007). It is ironic to note therefore that this combined product is still, even now, only commercially available in Australia and New Zealand.

Liggins also went on to show, in the same single, long, carefully conducted trial, that two 24 mg doses 24 hours apart were no more effective than the two 12 mg doses of the same product. Indeed, as several American obstetricians and paediatricians showed, in a whole series of animal and tissue culture experiments between 1970 and 1975, it takes only a modest dose of cortisol to trigger the sort of maturational process normally stimulated by labour and delivery, by occupying all the available cytoplasmic receptor sites. Lung lecithin production does not start to rise for 12 hours after cortisol is added to the tissue culture medium, and reaches a rate limiting maximum after 24 hours (Moore, 1976). The effect then persists for five days after cortisol is removed from the medium. These tissue culture findings mirror, to an uncanny degree, the findings in the 1135 women recruited into the clinical trial in Auckland, New Zealand between 1969 and 1974. While a range of other drugs and hormones, including heroin and thyroxine, can also speed lung maturation, none seem to be as potent as the glucocorticoids first studied, and no way has yet been found to further boost the effect caused by glucocorticoid administration. Observational studies also suggest that, while surfactant treatment *after* birth can augment, it cannot replicate, all the benefits associated with *antenatal* steroid administration (Jobe *et al.*, 1993), and 6 controlled trials completed since surfactants first became available confirm this. (Sir Graham Liggins died in New Zealand on 24<sup>th</sup> August 2010)

**Betamethasone vs dexamethasone:** While betamethasone was the product used in the first trial of antenatal steroid treatment that Graham Liggins conducted with his paediatric colleague Ross Howie, dexamethasone was the more widely used glucocorticoid in the UK for most of the next 25 years. Both drugs seem to be of comparable efficacy in most respects but while we know much about the later physical and intellectual development of the children born to the mothers recruited into the Dutch trial, and into the large, NIH-backed, collaborative trial in America, and even more about the children from the original trial from New Zealand, who have now been followed for 30 years, whose mothers were all given betamethasone, there is much less information on the subsequent children exposed to dexamethasone before delivery.

There are also two observational studies suggesting that, while antenatal treatment with betamethasone has no effect on, or may actually reduce the risk of subsequent cystic periventricular leukomalacia in the baby, repeated treatment with dexamethasone increases it (Baud *et al.*, 1999; 2000; Spinillo *et al.*, 2004). The mechanism underlying any such difference remains unclear, and it should be noted that women in these studies were not randomly allocated between the two treatment groups. However there is now experimental evidence in animals that sulphite, a preservative present in several commercially available brands of IV dexamethasone, can be neurotoxic (Baud *et al.*, 2001) so there are good grounds for using betamethasone rather than dexamethasone, and also for trying to use a sulphite-free product. While a recent small head-to-head trial (Elimian *et al.*, 2007) found no such difference (and less IVH in the dexamethasone group), another large retrospective review using non-randomised observational data collected by the American NICHD Neonatal Research Network (Lee *et al.*, 2006) has also found that there was a higher risk of neonatal death following maternal treatment with dexamethasone than there was following treatment with betamethasone. There was also more neurosensory disability in the two year survivors (Lee *et al.*, 2008). It is proving very difficult to decide whether these differences are likely to have been due to the glucocorticoid used, or to the excipient that was present in some products. However a further large head-to-head trial involving a direct comparison between betamethasone and dexamethasone has recently been funded in Australia and New Zealand.

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## Repeated antenatal treatment

The value and the safety of giving more than one course of antenatal corticosteroids has been hotly debated for many years now. Early reports of increased neonatal mortality and of maternal and neonatal morbidity (e.g. Banks *et al.*, 1999) were offset by other reports of an improved neonatal pulmonary outcome with no compensatory disadvantages. An NIH consensus conference in 2000, re-endorsed by the American College of Obstetrics and Gynecology in 2008, concluded that “*Data from studies on both animals and humans raise questions about the safety of repeat doses of antenatal corticosteroids. Animal studies have shown that repeat courses of antenatal corticosteroids have deleterious effects of lung growth and organisation, cerebral myelination, the function of the hypothalamic-pituitary-adrenal axis and retinal development. In addition, there is evidence for a dose-dependent effect on fetal growth and persistence of immature lung architecture.... Data from currently available studies assessing benefits and risks are inadequate to argue for or against the use of repeat or rescue courses of antenatal corticosteroids for fetal maturation.*”

However animal experimentation can only throw an indirect light on the probable balance of risk and benefit associated with repeated treatment as many have stressed (Jobe *et al.*, 1998), and the NIH consensus statement in 2000 sensibly concluded that controlled trials were urgently needed and that repeat use should generally be reserved for patients enrolled into such trials. Plans for a trial in the UK (the TEAMS trial) received pilot funding from Action Research in 1999 (Brocklehurst *et al.*, 2000), but failed to get substantive backing from the MRC in 2002 even though its design was highly rated, partly because the MRC’s research budget was tight but also because recruitment to the pilot study had proved more difficult than expected. The results of the initial small pilot study have never been made public.

One early US trial, recruiting women 24–32 weeks pregnant, was later stopped after 502 women had been recruited, because there seemed little prospect of it demonstrating any significant reduction in the trial’s composite measure of short term neonatal morbidity (Guinn *et al.*, 2001; Lee *et al.*, 2004) – a decision that was quite widely criticised (Murphy *et al.*, 2002). A Finnish trial, which also closed early after 249 women had been recruited, reported a post-hoc analysis that seemed to suggest that further treatment might actually do more harm than good if delivery occurs less than 24 hours after further treatment is given (Peltoniemi *et al.*, 2007). However such *post-hoc* analyses need to be treated with caution, and the only difference of any statistical significance was the finding that surfactant was given more often to the babies delivering within 24 hours of the mother receiving a single further 12 mg dose of betamethasone (47% *v.* 33%; odds ratio 2.17 [95% CI 1.22 to 3.83]). Many of these children were seen again at two years, and the findings then were all very reassuring (Pesonen *et al.*, 2009; Peltoniemi *et al.*, 2009) – treatment had not had any measurable impact on growth, on toddler temperament, or on the amount of neurosensory disability.

In all at least eight trials have now tried to address these issues. A Cochrane Review of the results from five of the trials appeared in July 2007 (Crowther and Harding, 2007) and this will be updated again soon. The first single-centre American trial by McEvoy *et al.* in 2002 was small, recruiting just 37 women, and a trial sponsored by the American NICHD Maternal-Fetal Medicine Network which originally planned to recruit 2,400 women (Wapner *et al.*, 2006; 2007) was stopped by the Data Monitoring Committee after 495 women had been enrolled because of a marginal difference in the number of babies with a birth weight below the tenth centile (23.7 v. 15.3%), but the Australasian ACTORDS trial (Crowther *et al.*, 2006; 2007) managed to recruit 980 women as planned. Another small pilot trial in Canada (Aghajafari *et al.*, 2002) also led on to the funding of a very much larger study by the Canadian Institutes of Health Research (CIHR) – a trial that eventually studied a further 1,858 women from centres in 20 different countries (Murphy *et al.*, 2008).

No maternal problems were identified as a result of repeat treatment in any of these trials. There had been a suggestion that both maternal and neonatal infection might be commoner if the mother was offered repeated treatment, but there was no evidence of this in any of the trials. The outcome of the four trials that involved repeat treatment **once a week** that were available for analysis when the first Cochrane overview was published in June 2007 and this suggested that such a strategy reduced both the number of babies showing some sign of respiratory distress at birth (Relative Risk 0.82 [95% CI 0.72 to 0.93]) and its severity (RR 0.60 [95% CI 0.48 to 0.75]). However no evidence of any such benefit was seen in babies born to women receiving further steroid treatment **once every two weeks** in the large Canadian trial published 18 months later (Murphy *et al.*, 2008). While the fact that repeat treatment was only offered once a fortnight may well explain the difference in the trial's main outcome, the failure to find any evidence of benefit in the sub group who actually delivered within a week of treatment is harder to explain.

Much has been made of the fact that the actively treated babies in the Canadian trial weighed, on average, 113 grams less than the control babies at birth, and had slightly smaller heads, but almost all of this can be explained by the fact that the actively treated babies in this trial ended up delivering almost half a week earlier than the control babies (a difference not seen in the other trials). It has been suggested that this difference in birth weight is large enough to make repeat treatment unwise but, allowing for the chance difference in gestation at birth, the finding from the most recent trial actually only confirms what had already been established by four earlier trials and in these trials there was no evidence that the small difference in weight-for-gestation at birth had any detectable impact on later development or on long term growth.

There was certainly no difference in the developmental progress being made by the surviving children in the American and Australasian trials two years later, and no difference in height, weight or head circumference in the two groups at two years. While 4.5% of the babies in the Australian trial had some sign of cerebral palsy at two years (Crowther *et al.*, 2007), the proportion was almost identical in the two trial groups. There was marginally more overt cerebral palsy in those given four or more courses of treatment in the American NICHD funded trial (Wapner *et al.*, 2007) but the number was so small (5 v. 1) that this difference could well have arisen by chance. Nevertheless, because babies in the Australian trial seemed to derive just as much benefit as those in the American trial while receiving less steroid treatment (just one 11.4 mg dose of Celestone Chronodose once a week IM after the first full course of treatment), many may well decide to choose this strategy for the moment, while limiting repeat treatment to pregnancies where there remains a significant chance that the baby will have serious breathing problems at birth (generally only babies delivering more than ten weeks early).

A recent retrospective case control study (Chen *et al.*, 2008) found no evidence that repeat treatment had any significant impact on somatic growth at ten years, but such studies can never provide information that is as reliable or informative as that provided by a randomised controlled trial. This study did find a minor difference in head circumference, but it did not look at cognitive development. Luckily we should know how the children in the Australasian trial are doing at 6–8 years by the end of 2011.

However a paper summarising outcome to discharge for the 578 women recruited into yet another recent American trial has also now appeared (Garite *et al.*, 2009). In this trial women who had already had one course of betamethasone before pregnancy had lasted 30 weeks but then remained undelivered for more than 14 days were not offered further regular 'booster' treatment, but were given a further course of treatment (so called 'rescue treatment') as in Wapner's NICHD funded trial if it became clear that delivery was likely to occur within the next seven days and pregnancy had not yet reached 33 weeks gestation. In this trial, as in the trials summarised in the current version of the Cochrane Review, such treatment *did* significantly reduce a composite measure of neonatal morbidity.

Those who wrote the editorial that accompanied the publication of the Canadian (MACS) trial (Newnham and Sinnet, 2008) believed that the MACS trial's outcome provided clear evidence that women should not be given more than one course of corticosteroid treatment before delivery, and this conclusion was very widely reported in other medical journals. The conclusion is, however, flawed. The fact that this trial did not find any evidence of benefit does not invalidate the findings of the other trials that *did* show that repeat treatment at weekly intervals, or 'rescue' treatment once delivery again looks imminent, could be of real benefit to babies still immature enough to be at real risk of developing respiratory problems after delivery.

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## Dose and route of administration

The original trial strategy – two 12 mg doses of betamethasone phosphate 24 hours apart – has been more studied than any other, and it still remains the best. Giving treatment every 12 hours (four 6 mg doses 12 hours apart) confers no recognisable advantage if a long acting formulation is used (see above). This strategy seems to provide a dose high enough to bind most receptor sites (Ballard, 1995) while administering a dose that is only at the high end of the physiological range (Collaborative Group, 1981). The only study that has compared oral to IM treatment (which looked at dexamethasone rather than betmethasone) concluded that there were good reasons for sticking to the IM route (Egerman, 1998).

Liggins and Howie actually went on and studied what happened if they gave double the dose they used at the start of their first seminal ground-breaking trial after publishing the results of what they found after recruiting the first 282 women into their trial. They were unable to find any evidence that a higher dose was better, but this finding was never widely reported (Liggins, 1976). Indeed it could well be that a smaller dose would be equally effective but, until such time as there is some evidence that a single 24 mg course of treatment might be hazardous, it would be ethically difficult to put this to the test. It is equally possible that a single 12 mg dose is just as effective as two such doses 24 hours apart and that what is needed is **time** for the first dose to achieve its enzyme-inducing effect, and not the administration of a second dose.

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## Is antenatal betamethasone treatment ever harmful?

Most drug treatments end up being widely adopted as soon as short term benefit is established and long before the long term effects are known and, where the benefit of treatment is as dramatic as it can be with antenatal steroid use, the continued reluctance of some influential authorities to support even an single antenatal course of treatment (Steer, 2005) is hard to comprehend. What such skeptics would of course stress is that if treatment delivers dramatic but short term benefit to only a few of the babies treated (see graph below), but subtle long term harm to all the babies treated, the real risk benefit ratio may be very different from what it initially seems to be. Because treatment needs to be given at least 12–24 hours, and preferably 48 hours, before delivery it often ends up being given to mothers who do not end up delivering at all until pregnancy reaches term. People do need to be very confident therefore that they are not doing even a little harm to the many babies who never actually needed treatment anyway. Interestingly it is doctors with a surgical background who seem to show most concern on this score. Those who use pills more than the scalpel might fairly point out that the long term outcomes of some surgical interventions (such as with the ever-rising rate of Caesarean delivery) have been just as poorly studied.

Luckily earlier fears that *one* course of treatment before birth might have an affect on blood pressure in later life (Dessens *et al.*, 2000) were allayed by detailed long term follow up studies (Doyle *et al.*, 2000; Dalziel *et al.*, 2004 and 2005), and almost all the other studies of the longer term effects of a *single* course of treatment have, to date, been equally reassuring (Finken *et al.*, 2008). As has often been the case with other treatment strategies, studies in which the two groups being compared had not been recruited into a randomized trial (Dessens *et al.*, 2000) raised fears that could be quite robustly discounted once the outcome from children who *had* been recruited into a trial finally became available. It will be many years before we have comparable information on the long term outcome of repeated exposure, but the two year outcomes reported to date seem, in general, to be very reassuring.

Funding bodies are now becoming increasingly aware of the need to document long term outcomes, and prepared to support long term follow up. It is to be regretted therefore that many ethics committees are, in contrast, making this increasingly difficult and asserting that, even though families knew they were signing in to a study that would involve long term follow up, any document recording consent to such follow up is no longer valid after one or two years. This can make it very difficult to maintain contact with the families concerned even though they had been well aware that this was what they were signing up to and, if made to feel, from the outset, that they were *partners* in the research study, express nothing but pleasure when re-contacted again many years later.

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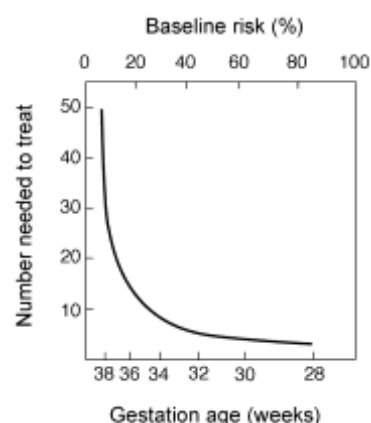
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## Gestational age at which treatment is effective

In the very first trial mounted by Graham Liggins antenatal treatment was offered to any mother who looked likely to deliver before 37 weeks gestation. When the results came to be analysed it was easiest to demonstrate benefit in babies delivering at 30–32 weeks gestation, and the large Collaborative trial in America came up with very similar findings. As a result most clinicians soon came to think that treatment was *only* appropriate for women likely to deliver at 30–34 weeks gestation, forgetting that absence of evidence of benefit is not the same thing as evidence of absence of benefit. Confusion was also triggered by the way in which the outcome of the American study was subjected to excessive (and not prespecified) sub-group analysis, and this confusion was compounded by the way the results were then interpreted (Robertson, 1982), and misreported (Philip, 1982), and by a failure to see the results of the US trial in the context of all the other results from all the other trials already available by then. This confusion was only finally dispelled when Patricia Crowley published the result of her systematic review of *all* the available trial data in 1990, and the NIH Consensus Development Conference met to review that evidence in 1994. That



conference had little difficulty in recommending that antenatal treatment should be offered to any woman likely to deliver at between 24 and 34 weeks gestation.

In fact there was, even then, little proof that such treatment was of benefit to babies of less than 28 weeks gestation. Relatively few of the babies in the early trials were born that early, and even fewer survived. There is, however, now substantial observational data (Salhab, et al., 2003; Foix-Hélias *et al.*, 2008; Tyson *et al.*, 2008) that seems to show that antenatal steroids are as good at reducing the incidence of respiratory distress in babies of less than 28 as there is in babies of more than 28 weeks gestation at birth. There are also at least two reports suggesting that the same is true of babies delivered before 24 weeks gestation (Abbasi *et al.*, 2007; Hayes *et al.*, 2008). Indeed, it rather looks as though giving antenatal steroids shortly before delivery halves the risk of respiratory distress developing after birth, irrespective of the gestation at which delivery occurs (Sinclair, 1995), and this may even be true of babies delivered by elective section at 37–38 weeks gestation (Sutchfield *et al.*, 2005). How many women need to be treated to prevent one baby developing respiratory distress seems to depend, therefore, merely on the base line risk without treatment. This number varies as gestation advances but is always substantially lower when the baby undergoes elective delivery before the onset of labour (see figure on page 5). The exact nature of the relationship is something that a new, freshly commissioned, Cochrane Review is currently addressing, but in babies of less than 30 weeks gestation least one baby seems to benefit for every three treated, while in babies of 36 weeks gestation five times this number need to be treated for one to benefit.

There can, if this relationship holds true, be no logical bar to administration in a pregnancy that seems destined to end before 24 weeks gestation. Nor is there any good reason not to give a single course of treatment in certain high risk situations when pregnancy has already reached 34 weeks gestation if it becomes clear that the baby is going to have to be delivered before labour occurs spontaneously since we know that babies delivered electively at 35–38 weeks gestation can, on occasion, develop respiratory distress from surfactant deficiency severe enough to require ventilatory support and a few have died (Madar *et al.*, 1999). It is never going to be possible to show that even a single brief course of antenatal steroid treatment is totally risk free, but the recent studies, reporting the follow up of a cohort from the original New Zealand trial after an interval of 30 years, make the existence of any major, still undetected, risk increasingly unlikely.

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### The continued absence of a licence for the best-studied product

Schering-Plough in New Zealand have a license to sell their product (Celestone Chronodose) for use antenatally to reduce the risk of neonatal respiratory distress (although the data sheet says that use beyond the 32nd week remains 'controversial' and that such use is contraindicated in 'pre-eclampsia, eclampsia or evidence of placental damage'). Unfortunately this product is not actively marketed outside Australia and New Zealand. No other pharmaceutical company ever seems to have asked for a license to market betamethasone (or any other steroid) for antenatal use in order to boost fetal lung maturation, and the regulatory authorities have never put pressure on any company to do this. As a result use in pregnancy still remains, after 20 years, an unlicensed use of a licensed drug for which the clinician has to carry full, undivided, legal responsibility. The general public find it difficult to understand why, when the regulatory authorities are prompt with advice on what constitutes potentially hazardous treatment, they seem so reticent to endorse good practice. The public perception is that, if a drug is not licensed for use for a

particular purpose, this must be because the authorities are not sure whether such use is appropriate or safe. The regulators for their part, see themselves as more like traffic police – they tell companies what they can *not* do, but never tell them where they should go, or what (in the public interest) they should do.

The *British National Formulary* has behaved in an equally cautious way. The nearest it has ever come to endorsing antenatal treatment is the negative statement that “there is no evidence of intra-uterine growth restriction following short-term treatment (e.g. prophylactic treatment for neonatal respiratory distress syndrome).” The length of time it took for this lifesaving intervention to come into general use is something of a scandal – an issue that was the subject of an instructive Wellcome History of Medicine Witness Seminar in 2005.

Reynolds LA, Tansley EM (eds). *Prenatal corticosteroids for reducing morbidity and mortality in preterm birth. Wellcome Witnesses to Twentieth Century Medicine, volume 25*. London: The Wellcome Trust Centre for the History of Medicine at UCL; 2005. (See also: [www.ucl.ac.uk/histmed](http://www.ucl.ac.uk/histmed))

### **Recent guidelines and consensus statements**

Among the more important consensus statements to appear in the last few years are an updated statement from the NIH in America, and a statement, endorsed by the World Association of Perinatal Medicine, which was published by Miracle *et al.* in 2008.

National Institutes of Health Consensus Statement. The National Institutes of Health Consensus Development Conference on the effect of corticosteroids for fetal maturation on perinatal outcomes. Effect of corticosteroids for fetal maturation. *Obstet Gynecol* 2008;**111**:805–7.

Miracle X, Di Renzo GC, Stark A, *et al.* Guideline for the use of antenatal corticosteroids for fetal maturation. *J Perinat Med* 2008;**36**:191–6.

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Last updated November 2009

## APPENDIX

## Sulphite content of certain glucocorticoid preparations

**Betamethasone:** The excipients in the more commonly used parenteral preparations currently on the market are said to be as follows :

**Celestone Soluspan<sup>®</sup>** (Schering Corporation). The 5 ml multidose vials contain a suspension of 15 mg of betamethasone as betamethasone sodium phosphate and 15 mg of betamethasone sodium acetate. The only excipients are sodium phosphate (52.5 mg), benzalkonium chloride (1 mg) and disodium edetate (0.5 mg).

**Celestone Chronodose<sup>®</sup>** (Schering-Plough Ltd). The 1 ml glass ampoules contain 5.7 mg of betamethasone [a mixture of 3.9 mg of betamethasone sodium phosphate (in solution) and 3mg of betamethasone acetate (in suspension)] and relevant quantities of the same excipients as Celestone Soluspan.

**Celestone Phosphate<sup>®</sup>** (Schering) The 5 ml ampoules contain 20 mg of betamethasone sodium phosphate solution (the equivalent of 15 mg of betamethasone base) The product contains the same preservatives as Celestone Soluspan.

**Betaject<sup>®</sup>** (Sabex). Each ampoule contains 3 mg betamethasone sodium phosphate, and 3 mg of betamethasone sodium acetate with the same excipients as Celestone Soluspan.

**Betnesol Injection<sup>®</sup>** (Celtech Pharmaceuticals Limited). The 1 ml ampoules contain 5.3 mg of betamethasone sodium phosphate (the equivalent of 4 mg of betamethasone base) with disodium edetate, sodium hydroxide, hydrochloric acid and **sodium metabisulphite** as excipients.

**Dexamethasone:** The excipients in the more commonly used parenteral preparations that are on the market, or were on the market until recently, are said to be as follows :

**Decadron<sup>®</sup>** (Merck Sharpe and Dohme Ltd). was for a long time one of the most widely used formulations in the UK. It contained **sodium metabisulphite**, sodium citrate, sodium hydroxide, methyl hydroxybenzoate, propyl hydroxybenzoate and creatinine.

**Decadron<sup>®</sup>** (Merck and Co Inc). There was **1 mg of sodium bisulphite**, 1.5 mg of methylparabens and 0.2 mg of propylparabens in each ml of this product. No such product is currently manufactured or sold in North America.

**Soludecadron<sup>®</sup>** is (or certainly was, until recently) available in France from Merck Sharp and Dohme-Chibret – it is known to have contained 0.15 mg/ml of **sulphites**

**Hexadrol<sup>®</sup>** (available until recently in the UK from Organon Technika) contained **sulphites** and **benzyl alcohol**. It is no longer said to be available in north America.

**Dexamethasone Sodium Phosphate** (available from Sabex both in north America and, intermittently, in the UK). The 4 mg/ml product contains **sodium metabisulphite**, methylparabens, propylparabens sodium citrate, sodium hydroxide and creatinine; note, however, that the 10 mg/ml product does **not** contain any sulphite preservative.

**Other generic products** A range of other generic products are intermittently available. Some, but not all, contain **sodium sulphite** and/or **benzyl alcohol** as excipients.