SCIENTIFIC DISCUSSION

1 Quality aspects

1.1 Introduction

Sodium oxybate is a simple molecule, the sodium salt of gamma-hydroxybutyric acid (GHB) and is presented in the form of a stabilised oral solution, 500mg/ml

1.2 Active Substance

Sodium oxybate is the Common Name of the substance butanoic acid 4-hydroxy-monosodium salt. At the time of writing this report there is no INN for this substance.

1.2.1 Manufacture

The manufacturing process is very simple and is basically a one-step hydrolysis of gamma butyrolactone under alkaline conditions with sodium hydroxide.

Starting materials and critical steps are well defined; there are no intermediates.

The active substance is obtained as a white solid which is dried, 'de-lumped' and packed.

The characterisation of the substance arising from the documented method of synthesis confirms that it is indeed sodium oxybate and this has been done by the usual range of spectroscopic methods including UV, IR & NMR together with elemental analysis and pKa determination.

Since sodium oxybate is to be given in solution, polymorphism has not been investigated

1.2.2 Specification

The specification includes test for identification (IR, HPLC), assay (HPLC), related impurities (HPLC) together with tests for water content (KF) residual solvents (GC) and heavy metals, all performed by validated methods. It is not necessary to control solid state properties.

The impurities include a number of named impurities and one un-named impurity, the levels of which have all been qualified on a toxicological basis and are considered to present no unnecessary risk.

Batch analyses (n = 45) from the site of manufacture defined in the dossier, demonstrate satisfactory compliance with the agreed specification and indicate good uniformity.

1.2.3 Stability

In addition to forced degradation studies in the solid state and in solution, stability studies have been performed on 6 batches of sodium oxybate under ICH conditions, accelerated and long term. No significant negative trends or out of specification results were observed in the formal ICH stability investigation, and on the basis of the accumulated results a satisfactory re-test period has been defined.

1.3 Medicinal Product

1.3.1 Pharmaceutical Development

The product is a simple aqueous solution which is stabilised with malic acid (hydroxysuccinic acid) and adjusted to the pH of maximum stability. From a microbiological point of view, investigations on this formulation showed that the product also had intrinsic antimicrobial activity and passed the test for efficacy of antimicrobial preservatives; therefore it was considered unnecessary to include a preservative in the formulation.

The product is presented as a plastic PET bottle with a child-resistant screw cap closure for the liquid, and in order to facilitate accurate dosage a separate dispensing or dosing system is attached at time of first use. This consists of a plastic adaptor to fit into the bottle, leading to a syringe dispenser allowing the patient to withdraw the accurate dose. In addition, two plastic dosing cups are provided with child-resistant closures.

The active substance is dissolved in purified water and the pH adjusted with malic acid before dilution with purified water, filtration, and bottling. The validation of this simple scheme was not problematical.

1.3.3 Product Specification

The product release specification includes relevant tests and limits for physical examination, identity

(HPLC & IR), assay (HPLC), impurities (degradation products, HPLC), volume in container, reproducibility of dosage, pH, microbiological attributes (PhEur), etc. Control of rheological properties is not considered necessary for a mobile liquid dosage form.

Batch analyses (n = 18) indicate satisfactory compliance with the agreed specification and satisfactory product uniformity

1.3.4 Stability of the Product

In all, ten batches of product have been investigated for stability under ICH conditions, accelerated and long term, and in all cases the results support the shelflife and storage conditions as defined in the SPC.

In addition, since this is a multidose product with a special adapter and dosing system, additional studies were performed with these plastic components in place, in order to mimic the in-use situation, and a suitable in-use shelflife has been defined.

In general the studies show that the plastic adapter and dosing system is compatible with the solution and does not encourage degradation.

Apart from the physical chemical analytical studies carried out during the stability investigations, microbiological studies were also performed with satisfactory results.

1.4 Discussion on chemical, pharmaceutical and biological aspects

The simple synthesis and manufacture of the product are described and controlled in a relevant manner, and the specifications of the active substance and medicinal product are considered to be relevant for a product of this type. The stability of the product has been well-investigated, both in the unopened form, and with the adaptor and dosing system in place during use.

Satisfactory uniformity of dose has been demonstrated, and there are no unresolved quality issues that could have an impact on the benefit/risk balance for the patient.

2 Non-clinical aspects

2.1 Introduction

2.2 Pharmacology

2.2.1 Primary pharmacodynamics (in vitro/in vivo)

Oxybate (GHB) is a metabolite of γ-aminobutyric acid (GABA) which is synthesised and accumulated by neurones in the brain. It is present at µM concentrations in all brain regions investigated as well as in several peripheral organs, particularly in the gastro-intestinal system. Neuronal depolarisation releases GHB into the extracellular space in a Ca2+-dependent manner. A family of GHB receptors in rat brain have been identified and cloned and most probably belong to the G-protein-coupled receptors. High-affinity receptors for GHB are present only in neurones, with a restricted specific distribution in the hippocampus, cortex and dopaminergic structures of rat brain.

In general, stimulation of these receptors with low (physiological) amounts of GHB induces hyperpolarisation in dopaminergic structures with a reduction of dopamine release. However, in the hippocampus and frontal cortex, GHB seems to induce depolarisation with an accumulation of cGMP and an increase in inositol phosphate turnover. However, at higher (therapeutic) exposures, GHB

induce dopaminergic hyperactivity, strong sedation with anaesthesia and EEG changes that are consistent with normal sleep and/or epileptic spikes.

The pathogenesis of narcolepsy is still unknown, but an imbalance between monoamines and acetylcholine is generally accepted. Recent research has found a marked reduction of the neuropeptide hypocretin type 1 in the cerebrospinal fluid of a majority of patients and a global loss of hypocretins in post-mortem brain tissue of narcoleptic subjects. The hypocretins are synthesised by a small group of neurones predominantly located in the lateral hypothalamic and perifornical regions of the hypothalamus. The hypothalamic system directly and strongly innervates and potently excites noradrenergic, dopaminergic, serotoninergic, histaminergic and cholinergic neurones. The effect of GHB on this system has not been investigated. However, the available data indicate that its mode of action is likely to relate to non-specific dopaminergic stimulation rather than the hypocretin system.

Formal nonclinical pharmacology studies to investigate the primary pharmacodynamics have not been conducted by the applicant, rather a comprehensive review of the scientific literature has been conducted. The publications included have been selected based on their relevance to the proposed indications, based on evidence of efficacy from early clinical studies. In addition, animal models of cataplexy and narcolepsy are continuing to be developed, but have not yet been fully validated. Little nonclinical information is available on its effects on narcolepsy in general, and cataplexy in particular. Available, directly relevant data, from the published literature, has been reviewed but the current understanding of the role of GHB in the CNS does not provide a mechanistic explanation of the positive clinical effects reported in the dossier. GHB had no effect on cataplexy in dogs with hereditary narcolepsy when administered as a single dose of 500 mg/kg i.v. or 50 mg/kg/day p.o. for 3 consecutive days. However, although such dogs have a mutation of the type 2 hypocretin receptor, the clinical relevance of this model remains to be established. Moreover, a dose of 75 mg/kg/day for at least 14 days is required for efficacy in humans.

Though the precise mode of action is unknown, the sedative properties of GHB and its effects on sleep may play a role in the efficacy observed in humans.

Evidence from a human clinical study (Study OMC-SXB-20) where GHB was administered to narcoleptic patients and overnight polysomnograms (PSG) were recorded, suggests that GHB modifies sleep architecture, specifically a dose-related increase in Stage 3 & 4 slow wave sleep (SWS, delta sleep). The cause of human narcolepsy and cataplexy is, as yet, unknown. Recent evidence points to the loss of hypocretin-containing neurones, possibly due to autoimmune attack, as a likely cause (Scammell 2003). Hypocretin is a neurotransmitter that has roles amongst others, in sleep-wake regulation. Alterations in hypocretin neurotransmission have also been observed in mouse and dog models of narcolepsy, although no studies have been undertaken with GHB in these models. Animal models of cataplexy and narcolepsy are continuing to be developed (Gerashchenko et al, 2003), but the effects of GHB in these models, have yet to be investigated.

2.2.2 Secondary pharmacodynamics

Published literature reports are presented that discuss the potential for effects on the respiratory, cardiovascular, gastrointestinal, renal and endocrine function, together with relevant findings from the toxicology studies.

GHB may increase growth hormone secretion, but this effect is inconsistent across species and dose levels. GHB has no other relevant secondary pharmacodynamic effects in animals.

GHB consistently decreases respiration by effects on minute volume and respiratory rate, with younger animals being more susceptible to these effects. In halothane-anaesthetized rats, GHB (187.5-750 mg/kg i.p.) dose-dependently decreased basal minute volume and respiratory rate compared to pre-injection control, with a maximum decrease to about 60% of pre-injection values for each parameter at the highest dose of GHB (Hedner *et al*, 1980).

Effects on cardiovascular parameters were also studied as part of the repeat dose toxicology studies in dogs, including heart rhythm and P-QRS-T complexes determined from ECGs, and there was no evidence of any dramatic changes in these parameters during the studies at doses up to 600 mg/kg/day (corresponding to male and female AUC0-24 of 3363.05 and 3631.35 µg·hr/mL and Cmax of 583.0

GHB administration on ECGs. The applicant claims that given the relatively long established clinical use of GHB, as an anaesthetic and sedative and other uses such as for the treatment of alcohol withdrawal, the undesirable effects and risk potential of GHB are well known, and additional nonclinical safety pharmacology studies are not justified. Results of some studies indicate weak rewarding effects and possible development of tolerance in rats and mice, however there is no compelling evidence that GHB represents a significant drug dependence hazard. Interaction of GHB with ethanol and other central nervous system depressants generally result in greater central depressant effects than seen with either drug alone. Numerous case reports of GHB poisoning demonstrate that overdosing in humans is associated with many of the same signs and symptoms as in animals: a rapid onset of drowsiness, nausea, vomiting, myoclonic seizures, respiratory depression progressing to apnoea, and coma.

2.2.3 Safety pharmacology

The applicant has not conducted animal safety pharmacology studies. However, there is ample evidence in the published literature that GHB is a potent CNS depressant, may cause convulsions and potentially fatal respiratory depression and cardiac failure.

On the basis of available information, the lack of conventional safety pharmacology studies is considered acceptable. However, since co-medication is probable, the effects of GHB on respiratory pattern in the presence of other CNS depressing agents like ethanol, and inhibitors of GHB metabolism like valproic acid and ethosuximide are mentioned in the SPC.
A weak tolerance to GHB administration has been demonstrated in a number of specific animal behavioural studies and also the development of cross-tolerance between GHB and ethanol. Therefore, potentially, an acute toxic effect (e.g. acute respiratory depression) could be experienced after drug intake following a period of drug withdrawal, sufficient for the disappearance of tolerance. Caution is advised if treatment is re-started after discontinuation. (SPC, section 4.2). Clinical data (open label study OMC-GHB-3) have failed to show any major development of tolerance on efficacy and the AUC after 8-weeks compared to the first dose was not significantly increased (study OMC-SXB-10, see clinical section). However, as these clinical data are too limited to draw firm conclusions, the potential for development of tolerance, especially with concomitant intake of ethanol, cannot be excluded and is mentioned in the SPC.

2.2.4 Pharmacodynamic drug interactions

Formal studies of pharmacodynamic drug interactions have not been conducted. According to the published literature, concomitant administration of GHB and other CNS depressants (benzodiazepines, barbiturates, alcohol) results in an additive increase in sedation.

2.3 Pharmacokinetics

The applicant has not conducted animal PK studies, with the justification that the more relevant pharmacokinetic data are derived from human exposure. Some data have been compiled from a review of the published literature. Data on non-clinical absorption, distribution, metabolism, and excretion have been compiled from a review of the published literature

2.3.1 Absorption- Bioavailability

In the rat, oral bioavailability was about 50-80%. Kinetics was non-linear, with oral dose increments resulting in an under-proportional increase in Cmax and an over-proportional increase in the AUC. By contrast, i.v. administration resulted in an over-proportional increase in Cmax. Thus, both absorption from the gut and elimination may depend on saturable mechanisms. Saturable absorption from the gut was confirmed in an everted rat intestine model.

2.3.2 Distribution

Whole-body autoradiography following i.v. injection of ^{14}C-GHB in mice showed a fairly uniform distribution pattern of radioactivity due to GHB and/or its metabolites. Shortly after injection, lower radioactivity was found in fatty tissues such as thymus, brown fat, and the white and grey brain matter

distributed throughout the body, including brain, skeletal muscle, myocardium, kidney, spleen, liver, lung, thymus, urinary bladder, stomach, intestines, and, in pregnant mice, the foetus. GHB distributed rapidly to the brain of rats, dogs and monkeys, producing brain concentrations several orders of magnitude above the physiological level. In the dog, the highest concentration was found in the white matter of the temporal lobe. There are no data on plasma protein binding in animals, but this is likely to be negligible.

2.3.3 Metabolism (in vitro/in vivo)

Metabolism of GHB is rapid and complete and proceeds via succinic semialdehyde, succinate and the Krebs cycle or through γ-hydroxybutyrate and β-oxidation.

The potential for inhibition of CYP isozymes was tested in pooled human liver microsome fractions using standard markers for CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A. In all cases, the IC50 was > 3000 µM (> 378 µg/ml). Since the average maximum human exposure is 142 µg/ml, GHB is not expected to show pharmacokinetic interactions with drugs metabolised by these isozymes. Non P450 mediated effects on GHB metabolism are unclear.

A rat study found that co-administration of compounds stimulating or inhibiting GHB dehydrogenase were able to decrease or increase plasma levels of GHB by up to 1/3. The interactions resulting from the stimulation or inhibition of GHB dehydrogenase, namely with anticonvulsivant drugs and L-dopa are considered to be clinically relevant and are mentioned in the SPC.

2.3.4 Excretion

Clearance is predominantly by biotransformation, with limited amounts of unchanged drug recovered from the urine or faeces. Radiospirometric studies in rats showed that 14C-GHB was rapidly converted to exhaled CO2 and about 2/3 of the dose was excreted by respiration within 6 hours and an additional 10- 20% over the next 18 hours. After oral administration of 14C-labelled GHB (200 mg/kg) to rats, the urinary recovery over 48 hours was 5.5% of the radioactive dose, and only 1.5% was recovered in the faeces. There are no data on the excretion of GHB in the milk of lactating animals. The proposed SPC contains an appropriate statement to this effect.

T½ in rats following oral administration of a single dose of 200 mg/kg was 0.75 h for the α- and 2.68 h for the β-phase. Similar T½ values were observed in dogs and monkeys. In rats, Cmax and AUC values tended to be higher in females than in males, whereas the opposite applied to dogs.

The applicant has been asked to discuss the comparative pharmacokinetics in humans and experimental animals and the implications for a critical appraisal of the relevance of the main species used in the toxicity testing for human safety assessment. In summary, the rat and dog showed similar pharmacokinetic characteristics, although exposure measured as AUC was higher in human than in either rat or dog at the NOAEL. The exposures measured in the maximum tolerated dose toxicokinetic studies (conducted in support of mouse and rat carcinogenicity studies) were, however, greater than in human subjects (Cmax 2.60- and 2.76-fold; AUC 1.21- and 1.64-fold for mouse and rat, respectively).

2.4 Toxicology

All toxicology studies were conducted by the applicant with the exception of data from literature for single dose toxicity and carcinogenicity in mice.

2.4.1 Single dose toxicity

Formal single dose toxicity studies were not conducted. A review of published literature data identified a number of references providing LD50 values in several species. In the mouse, LD50 values of 2960 – 3700 mg/kg following i.p. injection were identified; in the rat, LD50 values were 9990 mg/kg following p.o. administration, and 1700 mg/kg following i.p. injection. In the rabbit and dog, LD50 values in excess of 1000 mg/kg were reported following i.v. administration, which could be increased to over 7000 mg/kg with artificial respiration without lethality.

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