COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Acemap 20 mg tablets (penfluridol)

NL/H/5547/001/DC

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This module reflects the scientific discussion for the approval of Acemap 20 mg tablets. The procedure was finalised on 25 July 2023. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CAR	Conditioned Avoidance Response
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
DA	Dopamine
DOPAC	3,4-Dihydroxyphenylacetic Acid
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
EPS	Extrapyramidal Symptoms
ERA	Environmental Risk Assessment
HVA	Homovanillic Acid
ICH	International Conference of Harmonisation
i.v.	Intravenously
MAH	Marketing Authorisation Holder
MOPEG	3-Methoxy-4-hydroxyphenylglycol
NA	Noradrenaline
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
p.o.	per os = by mouth
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Acemap 20 mg tablets, from ACE Pharmaceuticals B.V.

The product is indicated for maintenance treatment of schizophrenia in adults.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC.

This decentralised procedure concerns a bibliographical application based on well-established medicinal use of penfluridol. For this type of application, the MAH needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years in the specific therapeutic use. The results of non-clinical and clinical trials are replaced by detailed references to published scientific literature.

Penfluridol tablets were first introduced into the European market at least ten years ago as a preoperative medication for maintenance treatment of schizophrenia in adults.

The MAH submitted a justification for bridging between their product and the product used in the literature, Semap 20 mg, tablets originally registered by Janssen (RVG 06603; licenced in 1973), based on comparable composition of the two formulations. The formulation was withdrawn on 5 July 2022 due to commercial reasons.

The concerned member state (CMS) involved in this procedure was France.

Scientific advice

The MAH has received scientific advice from the MEB twice (2013 and 2020), and an informal advice from the French National Agency for the Safety of Medicines and Health Products (ANSM) on the strategy to obtain marketing authorisation. It was indicated that due to the fact that Semap was not available anymore, a legal basis article 10(1) was not possible. As an alternative, a bibliographical application based on paragraph 5 of Article 10a of Directive 2001/83/EC, amended by directive 2004/27/EC, could be applicable.
Both regulatory authorities also advised on performing a pharmacokinetic study to assess all relevant pharmacokinetic characteristics of Acemap for bridging purposes to support relevance of the literature. Comparison of pharmacokinetic data obtained during the clinical trial performed by the MAH to available pharmacokinetic parameters described within the SmPC of Semap and the pharmacokinetic data available in scientific literature publications could be sufficient to substantiate bridging.

II. QUALITY ASPECTS

II.1 Introduction

Acemap is a white to-off white and biconvex round tablet. The tablets are fitted with a bisect score line on one side and engraved with the inscription “Acemap” on the other side. They can be divided into equal doses. Each tablet contains as active substance 20 mg of penfluridol.

The excipients are: lactose monohydrate, sucrose, maise starch, pregelatinised maise starch, crospovidone type A and magnesium stearate.

The tablets are packed in either a transparent PVC/PE/PVDC-Alu blister with 10 tablets in a carton box, or a white HDPE 50 mL container with child-resistant white PP closure with 50 tablets.

II.2 Drug Substance

The active substance is penfluridol, an established active substance although not described in the European, British or United States Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white crystalline powder. No polymorphism is known. The substance is practically insoluble in water, but freely soluble in methanol, ethanol, acetone and chloroform. Penfluridol has no chiral centres.

Manufacturing process

The manufacturing process of the active substance penfluridol starts with four raw materials. Via multiple intermediate materials, an intermediate in salt form is prepared. From this salt form, the drug substance penfluridol is prepared as a free base form. The free base is subsequently re-crystallised. Penfluridol is sieved through a sieve, and packed in double LDPE bag placed in HDPE container. This synthesis contains sufficient chemical steps (making or breaking of covalent bonds) and two purification steps. Several class 2 and 3 solvents are used in the synthesis, which are adequately controlled in the final active substance. Class 1 solvent carbon tetrachloride is controlled in one of the intermediate materials. The structure of the active substance has been adequately elucidated and reports, chromatograms, spectra and other results are provided. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Quality control of drug substance

The active substance specification by the MAH includes tests for appearance, identity, sulphated ash, heavy metals, loss on drying, related substances, assay, residual solvents, particle size distribution and microbial purity. The specification of the MAH is acceptable in view of the route of synthesis and the various European guidelines.
The analytical procedures of the drug substance manufacturer have been adequately described. The analytical procedures have been fully acceptably validated. Batch analytical

data demonstrating compliance with this specification have been provided for four commercial scaled batches.

Stability of drug substance

Stability data on the active substance have been provided for one pilot scaled batch and three commercial batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 18 months. Based on the data submitted, a retest period could be granted of 12 months when stored under the stated conditions.

II.3 Medicinal Product

Pharmaceutical development

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

The choice of excipients is justified and their functions explained. Solubility data of the active substance is pH dependant. The development has been based on similarity with the literature reference product Semap. The composition differs qualitatively with respect to talc and colourants. The pharmaceutical development of the product has not been adequately performed in view of bridging to the literature reference product. The lack of the *in vitro* dissolution data is overruled by these *in vivo* data for bridging. A pharmacokinetic study has been performed with a batch of a small number of tablets. In order for this product to be representative of commercial scale product, the maximum batch size is set to a big number of tablets.

Manufacturing process

The manufacturing process consists of wet granulation, wet sieving, drying of granule, sieving, mixing and blending with extragranular excipients and tabletting. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three commercial scaled batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph.Eur. requirements, except for pregelatinised maise starch. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identity, dimensions, weight, resistance to crushing, subdivision of tablets, dissolution, water activity, degradation products, assay, uniformity of dosage units and microbiological purity. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Appropriate tests for nitrosamine presence are performed on the final product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three commercial scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided from one pilot scale clinical batch (packaged in HDPE bottles with PP caps) stored at 25°C/ 60% RH (25 months) and 40°C/75% RH (9 months) in accordance with applicable European guidelines. In addition, stability data for three commercial scale batches at 25°C/60%RH (6 months) and 40°C/75%RH (6 months) packaged in HDPE bottles with PP caps and PVC/PE/PVDC-Alu blister packaging have been provided. Photostability studies are performed in accordance with ICH recommendations. On basis of the data submitted, a shelf life was granted of 12 months. No specific storage conditions needed to be included in the SmPC or on the label.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM for excipient lactose monohydrate have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Acemap has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Because Janssen Pharmaceutica obtained a market authorisation for Semap in 1973, based on their own non-clinical and clinical data, almost no relevant scientific literature presenting non-clinical data is available in the public domain. Therefore, 50 years of clinical experience and a well-known safety profile in the proposed patient population is the main bibliographical substantiation of this dossier.

III.2 Pharmacology

The pharmacological effects of penfluridol have been extensively described in the literature. Studies in animal models using mice, rats, rabbits, dogs and guinea pigs have been found. Penfluridol use in animal models for the intended indication is well-established in the literature.

Primary pharmacodynamics

Penfluridol was discovered in 1968 at Janssen Pharmaceutical and is an established first-generation antipsychotic used in the treatment of chronic schizophrenia and other psychotic

disorders. After oral administration penfluridol has a very long elimination half-life, up to one week. This allows for medication administration only once a week. Clinical research suggests that the appropriate dosage for penfluridol is 40 to 80 mg/week (Tuan et al. 2019). The primary pharmacodynamics of penfluridol is extensively explained in the Clinical Overview of Pharmacology. Since no recent nor high quality scientific literature is available on the primary pharmacodynamics of penfluridol, this topic will not be discussed extensively in the current section.

The mechanism of penfluridol's action against the positive symptoms of schizophrenia and other psychotic disorders is thought to be blockade of dopamine receptors, especially to postsynaptic D2 receptor. Penfluridol also acts as a T-type calcium-channel blocker (Kd value ≈ 70–100 nM) (Tuan et al. 2019).

Airaoldi et al. (1974) found that penfluridol is a powerful antagonist of amphetamine-induced stereotyped behaviour in rats and mice. Full protection was obtained for a 12 hour period, while at 24 hours there was 79% inhibition of amphetamine activity. The brain level of penfluridol necessary to exert a significant effect against amphetamine is therefore around 7 ng/g of brain.

Kuribara et al. (1975) studied the effects of penfluridol on operant behaviour were investigated and compared with those of chlorpromazine and haloperidol in rats trained on the following five schedules Fixed ratio (FR 30) of food reinforcement and differential water reinforcement of low rate (DRL 20 sec) schedules were used for positively reinforced behaviours. Continuous (Sidman-type) and discriminated avoidance schedules were used for negatively reinforced behaviours. Behavioural effects suggested that penfluridol has neuroleptic properties similar to those observed with chlorpromazine or haloperidol. However, in general, the inhibitory effects reached the maximum level approximately at 16 hour and lasted for two approximately three days after oral administration of the drug. Intensity of the effect of penfluridol was estimated to be about 1/8 approximately 1/10 that of haloperidol, according to the results obtained in the avoidance performances.

It seems possible that penfluridol also block action on serotonin receptors and M-choline receptors. Antipsychotic agents are believed to disrupt the process of the release and return neuronal uptake of a number of biogenic amines. Antipsychotic drugs competitively bind with dopamine receptors and block the action of dopamine on corresponding receptor sites, thus lowering psychotic activity. Central dopamine receptors are subdivided into D1, D2, and according to some sources, D3 receptors. These receptors have a high affinity for dopamine, but they differ in sensitivity to neuroleptics of various chemical classes (Vardanyan & Hruby 2006).

The pharmacological action of antipsychotic agents is very complicated. Besides the ability to change behaviour, these drugs also have a number of other central and peripheral effects. Antipsychotics or neuroleptics are used for intervention in patients with severe and chronic psychosis of an organic as well as induced nature. These drugs are used for controlling manic phases in manic-depressive psychosis such as relieving anxiety, fear, excitement associated with somatic diseases, controlling aggression, tics, and other unequal conditions (Vardanyan & Hruby 2006).

In mongrel dogs of either sex a study was undertaken to (a) determine the locus of the antiemetic action of penfluridol by comparing the effective antiemetic doses of penfluridol given via different routes, (b) determine the degree of penfluridol protection against a large number of emetic agents whose sites of emetic action are known and (c) elucidate the mechanism of the antiemetic action of penfluridol (Lee et al 1978).

Penfluridol, 1 mg/kg given by mouth (p.o.), was effective in preventing the emesis induced by apomorphine, 1 mg/kg intravenously (i.v.), for at least six weeks. During this period, the anti-apomorphine activity of penfluridol was identical to that produced after surgical ablation of the medullary chemoceptive emetic trigger zone. This dosage of penfluridol was therefore used to determine its antiemetic spectra against agents other than apomorphine. The animals were usually challenged with the 100% emetic doses of emetic agents prior to the administration of penfluridol. They were then tested again with the same agent one day after receiving 1 mg/kg of penfluridol intragastrically. If animals did not vomit with the original test dose, they were then challenged with a much larger dose, usually 3-10 times the previous one, three days later (Lee et al 1978).

The protective effect of penfluridol, p.o. or i.v., against apomorphine induced emesis. Penfluridol, at a dose as low as 1 pg/kg p.o., protected 5 out of 11 dogs from the threshold emetic dose of apomorphine (0.01 mg/kg i.v.) for an average of 2.5 days. Increasing the dose of penfluridol to 5 or 10 pg/kg markedly raised the percentage of protection and prolonged the duration of protection. The approximate 50% protective dose (PDs0) of oral penfluridol to 0.01 mg/kg of apomorphine was 1.5 pg/kg. The protective effect of penfluridol was sharply reduced when the apomorphine dose was increased to 0.03 mg/kg. 1 pg/kg of penfluridol exerted no protective effect in 5 dogs and the PDs0 was increased to 8.0 pg/kg (Lee et al. 1978).

Nose and Takemoto 1975 have investigated the effect of a number of psychotropic drugs on the concentrations of brain monoamines and their major metabolites, and attempted to see whether the long action of penfluridol in the pharmacological tests in animals also held for monoamine metabolism in brain. Earlier investigations have shown that a number of neuroleptics increase the concentration of homovanillic acid (HVA) but not that of 5-HIAA in animals and that phenothiazines used as minor tranquillizers have only a slight effect, or none at all, on the concentration of HVA in rat corpus striatum.
The data in mice support the findings cited above. Thus, all neuroleptics tested in this experiment caused an increase in the HVA concentration of mouse brain. Haloperidol was found to be the most effective in increasing the HVA concentration, and the relative potency of the drugs decreased in the following order: haloperidol > pimozide > chlorpromazine > penfluridol > oxypertine (Nose & Takemoto 1975).

Oral administration of penfluridol increased the HVA and 3,4-dihydroxyphenyda
lacetic acid (DOPAC) concentrations in rat corpus striatum as in mouse brain, though 6 hr after its administration, 10 mg/kg penfluridol caused a significant fall in the dopamine (DA) concentration of rat, but not of mouse, brain. The effect of 10 mg/kg penfluridol on the HVA and DOPAC concentrations was similar to that of 2.5 mg/kg haloperidol and the effect of penfluridol persisted longer than that of haloperidol though the former was slower" acting than the latter. Therefore, our results seem to provide biochemical evidence for the

pharmacological data reported by Janssen et al. (1970) in which they classified penfluridol as a long-acting neuroleptic drug. It has been reported that some neuroleptics enhance the cerebral turnover of DA and noradrenaline (NA). The next experiments were done to investigate whether penfluridol could increase the NA turnover. Previous experiments have shown that changes in brain NA turnover induced by neuroleptics can be estimated by measuring brain 3-methoxy-4-hydroxyphenylglycol (MOPEG) concentration and that MOPEG in rat brain is detected only as a sulphate ester (Nose & Takemoto 1975).

From these results it appears that penfluridol affects only central DA neurons and the increase in the concentration of brain HVA induced by penfluridol is probably not due to an unspecific inhibition of the elimination of phenolcarboxylic acid from the brain. This is likely as penfluridol did not cause an increase in the concentration of MOPEG which has been reported to rise after blockade of its transport from brain by treatment with probenecid. Furthermore, penfluridol probably does not increase the HVA concentration by a reserpine-like release and/or amphetamine-like liberation of DA from its tissue store because penfluridol increased the HVA level markedly without decreasing the concentration of DA. In conclusion, the penfluridol-induced increase in HVA concentration of brain is interpreted as an increase in turnover of neuronal DA following blockade of the DA receptors of the effector cells and the antipsychotic action of penfluridol in schizophrenia seems to be related more to the prolonged action on DA receptors than to that on NA receptors (Nose & Takemoto 1975).

Secondary pharmacodynamics

Penfluridol has anticancer effects against various cancer cell lines via several underlying mechanisms. For instance, in an orthotopic model of breast cancer, penfluridol suppressed breast cancer growth by 49%. More compellingly, penfluridol suppressed the growth of metastatic brain tumours, after breast cancer cells were introduced by intracardiac and intracranial injection, by 90% and 72%, respectively (Tuan et al. 2019).

D2-receptor antagonists showed biological effects against cancer in vitro and in vivo. Moreover, D2-receptor agonists increased phosphorylation at threonine 308 of Akt in neurons, and Akt phosphorylation is known to plays a vital role in cell proliferation; this suggests that D2- receptors are associated with tumourigenesis. Unlike D2- agonist, D2-antagonists decreased cell viability and encouraged apoptosis in several cancer cell lines in vitro (Tuan et al. 2019).

The molecular mechanisms of D2-receptor antagonists against cancer cell growth have been recorded in attractive therapeutic targets such as signal transducer and activator of transcription, receptor tyrosine kinase, Wnt, phosphoinositide 3-kinase, and mitogen-activated protein kinase/extracellular signal-regulated kinase. Recently, D2-receptor antagonists mitigated cell proliferation and induce apoptosis in vitro in various cancer cell lines. In addition, D2-receptor antagonists had potent effects in some cancer xenograft animal models, suggesting that D2-receptor antagonist may be used as a chemotherapeutic target. However, there is no direct evidence that the anticancer activity of penfluridol is due to D2-receptor antagonism. It is difficult to find a report explaining various mechanisms of anticancer activity involving of D2-receptor antagonism. In addition, penfluridol derivatives showed distinct anticancer and antipsychotic activities, thus suggesting that D2-receptor

antagonism may or may not contribute to the anticancer activity of penfluridol (Tuan et al. 2019).

A single subcutaneous injection of penfluridol (3 mg/kg) to rats elevated serum concentrations of prolactin for more than 96 h whereas it increased striatal concentrations of acid DOPAC and inhibited apomorphine-induced circling behaviour for less than 48 hours. The dose of penfluridol needed to elevate serum concentrations of prolactin (0.1 mg/kg) was less than that required to elevate striatal concentrations of DOPAC (1 mg/kg) or inhibit apomorphine-induced circling (3 mg/kg). Furthermore, the penfluridol-induced increase of striatal DOPAC was more susceptible to reversal by apomorphine than was the increase of serum prolactin concentrations. These results suggest that the dopamine receptors in the pituitary, which are normally activated by dopamine released from tuberoinfundibular neurons, are more sensitive to the blocking actions of systemically administered penfluridol than are dopamine receptors in the striatum (Annunziato et al. 1978).

Safety pharmacology

Both open and double-blind clinical studies have demonstrated the safety of the penfluridol as well as its effectiveness as an antipsychotic agent in the target population. Electroencephalographic studies suggest that the drug is free of epileptogenic properties. To date, no cardiovascular abnormalities have been reported among penfluridol-treated patients, in contrast to second generation typical antipsychotics. Most investigators have suggested that the optimal therapeutic dose level is between 30 and 40 mg per five to seven days. Although the major indication for penfluridol is the maintenance of chronic psychotic patients, a double-blind, placebo controlled study showed that penfluridol was also effective in psychotic patients described as acute (Ota et al. 1974).

Results of laboratory tests (haematology, renal function, hepatic function) and ophthalmologic and electrocardiographic examinations showed no abnormal changes in any of the patients. Analysis of vital signs during each of the six-day periods following drug administration showed no consistent pattern of change. However, a trend toward lower systolic blood pressure appeared over the entire treatment period, although this trend was clinically and statistically nonsignificant (Ota et al. 1974).

Ito et al. (1976) studied the neuropharmacological properties of penfluridol in experimental animals, compared with those of haloperidol and chlorpromazine. Locomotor activity of mice significantly decreased at doses of 16-32 mg/kg p.o. Like haloperidol and chlorpromazine, penfluridol (4-16 mg/kg p.o.) demonstrated catalepsy lasting for 48-72 hours in rats. Penfluridol strongly inhibited apomorphine-induced emesis in dogs and the ED50 was 0.016 mg/kg p.o. This effect lasted for 192 hours when administered 0.04 mg/kg po. Penfluridol antagnonised methamphetamine-induced stereotyped behavior in rats, ED50 was 1.83 ng/kg p.o., penfluridol also inhibited conditioned avoidance responses in rats, and the ED50's in the pole climbing and Sidman avoidance methods were 6.73 and 3.4 mg/kg p.o., respectively. Penfluridol neither inhibited motor coordination nor enhanced hexobarbital-induced anesthesia in mice. These results suggest that penfluridol is a potent and long-acting antipsychotic drug which has less neurotoxic side-effects than other first generation typical antipsychotics.

While penfluridol is considered to be a safe medication it is not without some side effects. Antipsychotic drug (ADP)-related hypothermia was first described by Loughnane. Although its underlying pathophysiological mechanism is not entirely clear, peripheral vasodilatation and a failure of central thermoregulation seem to play a role. In spite of its potentially fatal consequences, APD-related hypothermia has received substantially less attention than its clinical counterpart, ADP-related hyperthermia (Zonnenberg et al. 2019).

Ahlenius et al. (1973) looked at the possibility that penfluridol interacts with the development of catecholamine mechanisms in the brain at a sensitive developmental period, and thereby influences later performance. Rats of the Sprague-Dawley strain were used. All animals were born in the department and the time of birth noted within 12 hours. The nursing mothers in two of the litters were given penfluridol, 1 mg/kg, orally at day 1, 3 and 5 after delivery. Penfluridol was dissolved in a few drops of glacial acetic and the final volume was made up with 5.50/0 glucose. The nursing mothers of the three other litters received 5.5% glucose, orally at corresponding time intervals. The administered volume was kept constant at 5 ml/kg. The acquisition of a conditioned avoidance response was measured by means of a two-way shuttle-box. The rats were trained to avoid an electric shock in the box, with the sound of a house buzzer as warning stimulus. The conditioned stimulus (CS) was the sound of the house-buzzer, randomly delivered with a 0.5-2.5 minute interval. The unconditioned stimulus (UCS) consisted of an intermittent shock (50 tiz, 700 V), delivered through the grid floor of either compartment over a great internal resistance (270 kOhm) in order to diminish the influence from the animals own resistance. The following variables were then recorded: conditioned avoidance response (CAR), escape, escape failure, spontaneous crosses.

The infants of mothers given glucose started with 75~ CAR and reached 100~ CAR from the third training session. The infants of mothers given penfluridol showed an initial avoidance responding of only 35 ~ and after the fifth session they had reached the level of 90 ~ avoidance responding. During every session a significant difference appeared between control and treated animals. There was no disruption of the escape responses in any of the two different groups. No difference in spontaneous crosses were observed between the two groups (Ahlenius et al. 1973).

In order to investigate the duration of the action of penfluridol a separate experiment was performed. Sprague-Dawley rats of four weeks of age were trained to perform a CAR and then given a single dose of penfluridol, 1.0 mg/kg intraperitoneal, and the resulting impairment of the CAR lasted no more than 48 hour (Ahlenius et al. 1973).
There was no difference in the weight at the start of training four weeks after birth between the "control" group and the "penfiuridol treated" group ($p \sim 0.05$). Interestingly, the "penfluridol-treated" animals were found to be heavier than controls ($p \sim 0.001$) eight weeks after birth (Ahlenius et al. 1973).

The impaired avoidance in responding was in all probability not due to persistance of the drug during this time, since treatment with penfluridol resulted in an impairment of the CAR that did not last more than 48 hour. The finding of an increase in body weight in the "penfluridol-treated" rats is interesting in view of earlier findings that direct intra-hypothalamic injections of chlorpromazine have been reported to stimulate food intake in adult rats (Ahlenius et al. 1973).

There seems to be a time difference of functional development between noradrenaline and dopamine neurones. Results from experiments investigating the gross behavioural response of neonatal and young rats to noradrenaline or dopamine receptor stimulating agents and analysing the disappearance of noradrenaline and dopamine after inhibition of the tyrosine hydroxylase step indicate that the dopamine-containing neurons gradually develop their functions postnatally, whereas the noradrenaline containing neurones are more mature at birth have found that treatment with the catecholamine receptor blocking agent penfluridol, which seems to have a preferential effect on dopamine-receptors (Janssen et al., 1970), during early postnatal life interfered with the acquisition of a conditioned avoidance response in rats (Ahlenius et al. 1973).

III.3 Pharmacokinetics

Distribution

The distribution of a drug in the body is a function of its binding to plasma proteins and tissue components. Accordingly, if a drug is highly bound to plasma proteins, as is the case with the antipsychotic drugs, its apparent volume of distribution can be considerable if tissue distribution and binding are high (Balant-Gorgia & Balant, 1987).

The neuroleptics are lipophilic drugs, a condition probably important for their crossing the blood-brain barrier. They bind to many tissue components and dissolve in adipose tissue. These 'silent receptors' are important for the pharmacokinetic behaviour of neuroleptics. The hepatic extraction coefficient of antipsychotic drugs is high, as is their systemic clearance (about 30 to 60 L/h). Elimination half-life values around 24 hours are obtained only because the apparent volumes of distribution are about 100 L. This is important if peak and trough concentrations at steady-state are to remain within reasonable limits (Balant-Gorgia & Balant, 1987).

Airoldi et al. 1974 treated rats and mice with penfluridol 0.5 mg/kg, i.v. Penfluridol did not accumulate in the brain. In fact, the peak level of penfluridol and its rate of decline in the brain were almost coincident with the same kinetic parameters in the blood. There was a marked storage of penfluridol in epididymal adipose tissue. As a remit the levels of penfluridol in adipose tissue were still measurable 96 hours after drug administration but were not detectable (< 2 ug/ml or g) in the blood and in the brain 48 hours after penfluridol injection; the levels of the drug in the adipose tissue were about 100 times those in blood. The brain showed a relatively homogeneous distribution although at 1 hour, penfluridol was more concentrated in the hemispheres than in any other brain area while at 24 hours the concentration was least in the diencephalon. The rate of release of penfluridol in the adipose tissue was relatively slow and the drug was still measurable 72 hours after penfluridol administration.

No preferential accumulation of penfluridol in the various brain areas examined and including hemispheres, striatum, diencephalon, mesencephalon and cerebellum, was observed at short (1 hour) or longer times (24 hours) after penfluridol administration. A relatively high level of penfluridol in the epididymal adipose tissue of rats and mice was observed. In rats at 24 hours penfluridol concentration in adipose tissue is about 100 times the level present in blood while in mice at 12 hours the ratio between the level of penfluridol in adipose tissue and in blood is about 50 (Airoldi et al. 1974).

Metabolism

Studies conducted with 3H-penfluridol show that peak plasma concentrations of the unchanged drug accounted for less than 10% of the total radioactivity (Migdalof et al. 1979). This suggests that there is extensive first-pass metabolism. That concentrations of intact penfluridol were detectable in plasma at least 28 days after a single 20mg oral dose suggests the drug is very slowly eliminated once it reaches the systemic circulation. This hypothesis was confirmed by Malmgrem and Heykants (1976) who found an apparent elimination half-life of about 120 hours (Balant-Gorgia & Balant, 1987).

The main step in the metabolism of penfluridol is cleavage of the molecule by oxidative N-dealkylation. One moiety (containing the chloro group) does not appear to undergo further biotransformation. The other part (with the 2 fluorophenyl groups) is further metabolised by fj-oxidation and by conjugation. The metabolites have no clinical relevance (Balant-Gorgia & Balant, 1987).

Excretion

Approximately 30% of the weekly dose is excreted unchanged in the feces and less than 0.25% in the urine. The metabolites do not contribute to the neuroleptic activity of penfluridol. The elimination half-life is 4-7 days at once weekly dosing (Semap SmPC).

III.4 Toxicology

An understanding of the toxicities of neuroleptic agents necessitates a knowledge of the pharmacology behind their efficacy, as their toxicities are often an extension of their mechanisms of action.

Repeat-dose toxicity

Hepatotoxicity specifically linked with penfluridol use has not been described in scientific literature. Nevertheless, this phenomenon has been described in other antipsychotics medication.

The precise pathogenesis of liver damage with the use of antipsychotics is unknown. Several hypotheses have been proposed, but no unique mechanism has been detected since first generation antipsychotics and second generation antipsychotics comprise a group of molecules with largely different chemical structures, pharmacokinetics, and pharmacodynamics. Continuous use of antipsychotics is associated with abnormal liver function tests in up to 78% of patients. Generally, such alterations consist of elevated transaminases or cholestatic indices, which often occur within the first six weeks of treatment, remaining stable or resolving with continuous treatment. Although asymptomatic liver enzyme abnormalities may be common, significant liver enzyme elevations are rare, but can occur (Solmi et al. 2017).

During the first three years of antipsychotic treatment in patients with the first-episode schizophrenia, nonalcoholic fatty liver disease was associated with the presence of the major components of metabolic syndrome. Predisposing factors to liver damage include not only older age, high daily dosage/ serum concentrations, alcohol abuse, and a history of hepatic disease, but also some of the evidence-based combination treatments for borderline personality disorder, such as valproate (Solmi et al. 2017).

Drugs with strong anticholinergic properties low-potency first generation antipsychotics, can induce acute urinary retention, but urinary acute retention can also occur with ZIP or RIS, via central dopaminergic and serotoninergic mechanisms (Solmi et al. 2017).

Carcinogenicity

In two recent reviews, no causal linkage has been demonstrated between cervical and breast cancers and antipsychotics (Solmi et al. 2017).

Reproductive and developmental toxicity

Sexual dysfunction is frequent during antipsychotic treatment and can be due to several factors, including co-treatment with two dopamine D2 antagonists, long duration of illness, and TD in schizophrenia. Hyperprolactinemia can cause sexual and reproductive system dysfunction, including decreased libido, erectile dysfunction, and anorgasmia, as well as reproductive system dysfunction, such as gynecomastia, galactorrhea, and oligo- or amenorrhea in women. All antipsychotics raise prolactin levels (Solmi et al. 2017).

Ahlenius et al. (1973) investigated the effects of penfluridol (by Janssen et al. 1970) given to the nursing rat mothers, on the acquisition of a conditioned avoidance response (CAR) in the offspring four weeks after birth. Penfluridol given to nursing rat mothers on days 1, 3 and 5 after delivery resulted in an impaired acquisition of a CAR in their offspring when measured four weeks after birth. The impaired avoidance responding was in all probability not due to persistence of the drug during this time, since treatment with penfluridol resulted in an impairment of the CAR that did not last more than 48 hours. Neither can the impairment of the CAR be secondary to a malnutrition at the time of treatment or later. Both groups weighed the same at four weeks of age, i.e. at the time of training. Further, there was no weight loss in the mothers during the time of drug administration. However, the "penfluridol-treated" animals were significantly heavier than controls eight weeks after birth. Whether the increased weight in the "penfluridol-treated" rats reflects a lesion in developing areas regulating food intake remained unclear. Effect of penfluridol may be due to an impaired development of central catecholamine mechanisms which are involved in the acquisition of avoidance behaviour and 2) result in a decreased functional activity in the central monoamine neurons, especially in the limbic system (Engel and Lundborg, 1974) in their offspring, four weeks after birth.

Ahlenius et al. (1977) also found that neonatal penfluridol treatment produces deficits in the acquisition of an active avoidance response, an increased locomotor activity prepuberally followed by an abnormally decreased activity postpuberally, and an impaired ability to habituate novel stimuli. This behaviour changes were associated with decreased functional activity in the mesolimbic dopamine system at four weeks of age (prepuberal age). Because learning deficits could be counteracted by the increasing functional activity in of the catecholamine neurons with amphetamine, involvement of the central dopamine system was proven.

III.5 Ecotoxicity/environmental risk assessment (ERA)

The environmental risk assessment is adequate.

III.6 Discussion on the non-clinical aspects

This product has been granted a market authorisation for well-established use. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Penfluridol is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature.
Additionally, the MAH has performed a bioavailability study with its own penfluridol formulation.

IV.2 Pharmacokinetics

Bridging
A bioavailability study has been submitted, in which the single dose pharmacokinetics of penfluridol is evaluated after administration of 20 mg (1 x 20 mg Acemap tablets) and 40 mg (2 x 20 mg Acemap tablets) penfluridol.
Very limited penfluridol pharmacokinetic data are reported in literature. The reported t_{max} values are in the range of that observed for Acemap (7 hours). A large range of C_{max} values is reported, which is contributed to the fact that single dose and multiple dose data are reported, different formulations are used which may likely impact the rate of absorption and due to a large inter-individual variability in C_{max}. Next to that different analytical methods are applied and between laboratory variability should also not be excluded. The literature reported C_{max} after administration of Semap in literature (which may be considered a relevant formulation for bridging) is about 2-fold higher than those observed with the MAHs formulation in the study. However, in the study, single dose data are obtained while in the specific study, steady state data are presented. Considering the elimination half-life of up to seven days, accumulation can be expected after weekly doses resulting in higher C_{max} values as reported in literature. AUC values are not presented.
To further support the bridge to literature, the MAH provided simulate steady state data for the 20 mg Acemap formulation at the 20 and 40 mg dose, based upon the results of the single dose study. These simulated steady state pharmacokinetic data of the 20 and 40 mg single dose pharmacokinetics obtained with the Acemap formulation showed that these data are comparable to the steady state data obtained after administration of Semap (formulation used in Malmgren and Heykants (1976)). Bridging is therefore sufficiently supported.

Absorption
After single dose administration of 20 mg and 40 mg penfluridol (40 mg as 2 x 20 mg Acemap tablets), t_{max} values are observed at about 7 hours after administration. Over the dose range

of 10 - 20 mg, and based upon C_{max} and AUC_{0-t}, dose proportional pharmacokinetics is observed. AUC_{0-inf} tends to indicate a less than dose proportional increase, however a straight conclusion is hampered due to a relatively large extrapolated AUC. Dose proportional steady state pharmacokinetics are reported in literature.
Apparently, no information on the effect of food on the pharmacokinetics of penfluridol tablets is available. As it cannot be excluded that food may affect the absorption of penfluridol, a statement has been included that patients should take the tablets consistently with regard to food intake.
Penfluridol is subject to a high inter-individual variability. Based upon the study, after single dose the inter-individual variability at the 20 mg dose was 74% for C_{max} and 57% for AUC_{0-t} and at the 40 mg dose 47% for C_{max} and 37% for AUC_{0-t}.

Distribution
Protein binding of penfluridol is high, i.e. estimated to be about 98%. Penfluridol is distributed to fat tissues and crosses the blood-brain-barrier.

Metabolism
Penfluridol is extensively metabolised through cleavage of the molecule by oxidative N-dealkylation at the tertiary amine into a diphenylbutyric acid metabolite. This metabolite is further metabolised into a β-glucuronide by β-glucuronide conjugation and into an acidic metabolite.
The specific enzymes involved in penfluridol metabolism are not reported, although the SmPC of Semap indicated CYP3A4 is involved in the metabolism.

Elimination
After a single labelled 20 mg dose, penfluridol is excreted for about 30% in urine and 15% in faeces, mainly as metabolites. Less than 1% of the dose was recovered as unchanged penfluridol in the urine, and only about 4% of the dose was recovered as unchanged penfluridol in faeces, indicating that penfluridol was extensively metabolised in man. Elimination of radioactivity was slow, and only about half of the administered radioactive dose was recovered in urine (about 30%) and faecal extracts (about 20%) in the first seven days. The diphenylbutyric acid metabolite, which was excreted only in urine, was found primarily as its β-glucuronide conjugate. The acidic metabolite was found unconjugated in both urine and feces.
The elimination half-life is about 4-7 days.

Special patient groups
Limited data are available on the use of penfluridol in elderly. Elderly may be more sensitive to the use of penfluridol.
Limited data are available on the use of penfluridol in patients with renal impairment and hepatic impairment. Penfluridol is extensively metabolised and literature data indicated that

penfluridol is mainly excreted as metabolites with urine and faeces. However, the mass balance is incomplete.
No data are available in the paediatric population. Therefore, the use of penfluridol is not recommended for patients under the age of 18.

Interactions
No information seems to be available on which enzymes are involved in the metabolism of penfluridol, or which transporters are involved in the distribution. In addition, no information is available which enzymes and transporters are possibly inhibited by penfluridol. The SmPC of Semap indicates that CYP3A4 is involved in the metabolism.

As penfluridol is extensively metabolised, it is agreed that enzyme inducers may decrease plasma concentrations of penfluridol.
As no information is available on the possible inhibition of enzymes by penfluridol, this has been included in the SmPC.

IV.3 Pharmacodynamics

Primary pharmacodynamics
The MAH has provided an overview of the mechanism of action of penfluridol. The inhibitory activity of penfluridol is strongest on dopamine receptors D5, D3, D1 and D2, however penfluridol has high binding affinity to several other central nervous system targets as well. It should be noted though that the actual data on penfluridol is quite scarce and the potential role of serotonin receptor and calcium channel inhibition in the effect of penfluridol in patients with schizophrenia is unclear. Overall, there are no data in which the link between effect on receptor level and clinical outcomes would be established.

Secondary pharmacodynamics
The MAH has provided an discussion on secondary pharmacodynamics of penfluridol. As with primary pharmacodynamics, supporting data is scarce and clinical claims are mainly based on theoretical grounds. Penfluridol, as all antipsychotics exerting their effect via the dopaminergic system, can cause extrapyramidal symptoms (EPS) or hyperkinetic disorders. 5HT-receptor antagonist activity of penfluridol theoretically may counteract some of the EPS due to D2 inhibition.
Penfluridol can also interfere with prolactin secretion. The potential of penfluridol to inhibit prolactin release via its effect on calcium channels and 5HT receptor has been suggested based on penfluridol's inhibition activity shown in *in vitro* studies.
Penfluridol is not a strong inhibitor of histamine receptors or alfa adrenergic receptors. Nevertheless, adverse events associated with inhibition of histamine and alfa adrenergic receptors have also been reported for penfluridol and are included in the proposed SmPC. There are no data suggesting that penfluridol would have strong anticholinergic properties.

Pharmacodynamic interactions
The MAH has also listed a number of pharmacodynamic interactions, which are based on the adverse event profile of penfluridol or (typical) antipsychotics as a class, theoretical grounds or clinical evidence.

IV.4 Clinical efficacy

Penfluridol vs placebo / typical (oral/depot) antipsychotics

The main body of evidence for the efficacy of penfluridol in the treatment of schizophrenia comes from a Cochrane review performed by Soares & Lima (2006). This review and analysis included 27 studies, comparing penfluridol to placebo, another oral typical antipsychotic or an injectable depot antipsychotic. 82% of the studies were performed in the seventies where the design of studies in schizophrenia e.g. clinical endpoints among others was not well-established.

All studies were performed in adults, and the majority in patients with the diagnosis of chronic schizophrenia. The studies were in general small, and of limited quality in terms of reporting their methods (randomisation, blinding).

Efficacy outcomes were mostly dichotomous and scale derived data were mostly unusable for the meta-analysis. The main efficacy outcome chosen for the Cochrane review was 'no marked improvement', derived from Clinical Global Impression, dichotomised in 'no improvement or worse'. As a second efficacy outcome, 'needing additional antipsychotic' was used. The authors also analysed the risk of leaving the study early.

The quality of the studies or their reporting is clearly not up to current standards. Risk of bias is unclear in the majority of studies due to poor reporting of methods. Furthermore, it should be taken into account that the sample size of the studies was small.

The results of the Cochrane meta-analysis (2006, updated 2012) suggests that as compared to placebo, penfluridol has a statistically significantly lower risk for no improvement or need for an additional antipsychotic. In terms of leaving the study early, the results were inconclusive. As compared to other oral typical antipsychotics, there were no statistically significant differences between the groups in any of the efficacy outcomes. Versus depot antipsychotics, penfluridol was more favourable in terms of leaving the study early. However, no statistically significant difference forms no argument for an absence of a difference with the comparator and therefore equal effect. In this respect, it is questioned whether conclusion can be drawn at all in absence of a placebo as therefore assay sensitivity is not guaranteed.

Brief Psychiatric Rating Scale could only be analysed for one study versus an another oral antipsychotic. No statistically significant differences between penfluridol and oral fluphenazine were observed in endpoint scores. Note, the analysis was thus not for a change from baseline to end of study, and the same comments regarding strength of conclusions in absence of a placebo arm and non-inferiority margin as mentioned above, apply also here.

The Cochrane review concludes that although there are shortcomings and gaps in the data, there appears to be enough overall consistency for different outcomes. This conclusion can be endorsed. Whereas the endpoints of the meta -analysis are not the endpoints of efficacy expected in schizophrenia studies today, these endpoints indirectly reflect efficacy and patient's benefit. Especially the need for additional antipsychotic indicates insufficient psychotic control. As penfluridol clearly separated from placebo in both no marked improvement and need of additional antipsychotic the efficacy of penfluridol in schizophrenia

is considered proven. Result of the studies with an active comparator do not allow a conclusion that efficacy of penfluridol is comparable to that of atypical antipsychotics, From a methodological point of view a non-inferiority approach should have been followed. If this had been implemented it is likely that based on the confidence intervals presented that probably non-inferiority versus other antipsychotics would not have been concluded. For what this conclusion is worth as in absence of a placebo arm the studies have lack of assay sensitivity.

Overall in the context of previous registration of penfluridol and decades of experience with it, the provided evidence on efficacy is considered sufficient for the reasons stated above.

The patient population in the studies included concern mainly patients with schizophrenia diagnosis. In most cases it is not clear based on which criteria this diagnosis has been done. However it is clear that there are no studies in which patients suffering from recurrent or chronic psychosis outside of schizophrenia would have been included. The indication is therefore limited to *maintenance treatment of schizophrenia*.

The products/formulations used in the studies were not always specified, however when this data was available, the manufacturer of penfluridol was in all cases Janssen or McNeil Pharmaceuticals, which was part of Janssen already in the seventies. Therefore it is considered that Semap, by Janssen, is the most suitable product for bridging to the literature in this well-established use application.

Depot vs oral / Non-adherence

The MAH has also referred to a recent study by Van der Lee (2021), a retrospective cohort study, which shows that long term discontinuation rates are comparable between penfluridol and depot antipsychotics. The reciprocal i.e. retention rate may be interpreted as a coarse indicator of B/R as patients who benefit for whatever reason (efficacy, safety or other reasons) stay on treatment Hence this study provides some support for the findings of the Cochrane review on comparable efficacy between penfluridol and depot antipsychotics. However this was a retrospective observational study i.e. the choice of treatment is based on clinical characteristics of patients, and therefore the groups are not entirely comparable.

The proposed posology is in principle agreed. The starting dose in the majority of studies was 20 mg per week and titrated to response. The most common dose range in the studies was 20-60 mg per week, however a considerable number of studies had an upper dose of 120-160 mg/week. Nevertheless the mean dose reported across the studies was much lower i.e. ~40 mg/week. Considering the interindividual differences in PK, an optimal dose range, appropriate to all patients is difficult to establish. Titration according to response is therefore accepted, with the advice on careful supervision if doses higher than 100 mg per week are used. Not all tested batches passed the test for breakability indicating that the score line on the tablet is not always functional, i.e. doses lower than 20 mg cannot be accurately given. However, the MAH will only release batches that pass the test for breakability and thus have a functional score line, the SmPC posology can include doses lower than 20 mg, This is considered very welcome, given the individual need of dose titration, in particular in the elderly and also in patients switching from other antipsychotics to Acemap. The starting dose is 10-20 mg per week, which is endorsed.

Considering the variability in PK between patients and once per week dosing combined with the down titration of concomitant antipsychotics, the risk of relapse may be high in patients switching from another antipsychotic to penfluridol. However, the available literature references touching upon switching from other antipsychotics to penfluridol do not give precise advice on up- and down-titration. The MAH refers to the switching tables from Psychiatrienet in the Netherlands, which are based on haloperidol equivalent doses. However, as the validity of the advice given in Psychiatrienet cannot be verified. Therefore a general advice on gradual up- and down-titration is given in the SmPC .

Special patient populations

There are no data available in children and adolescents or the elderly, this is addressed in the SmPC.

There are no specific efficacy data in elderly supporting a specific dose. Reducing the dose in elderly from safety reasons in principle could be agreed. As the dose is titrated according to individual response on efficacy and safety, the current advice on careful monitoring of elderly due to specific adverse events in considered appropriate.

IV.5 Clinical safety

The MAH has provided an overview of the safety profile of penfluridol, based on literature data and post-marketing data with Acemap.

Adverse events

The most common adverse events are those known for (typical) antipsychotics, i.e. EPS, sleep disturbances, somnolence, dizziness, motor dysfunction and gastrointestinal effects. With respect to EPS, it should be noted that as the studies referred to are relatively old, the articles do not always give very specific information on the EPS observed and also cluster symptoms together without specifying number of patients per symptom. Therefore the estimation of frequency carries some uncertainty. Also the frequency of administrating antiparkinsonian medication in the studies should be assessed in the context of the age of the studies, as in some studies these were administered as standard and/or with seemingly low threshold. However in general, it can be observed from the studies that in many cases, mild to moderate EPS, such as akathisia, tremor, parkinsonism and muscle rigidity, occurred in a proportion of patients during the first 1-2 weeks of treatment, thereafter subsiding, which in some cases was treated with an antiparkinsonian medication. It is noted that while treatment with anticholinergics to control EPS caused by antipsychotics may have been standard practice in the seventies when treatment options were sparse, it is not rationale drug therapy of today. Currently a switch to another antipsychotic causing less EPS is a better solution, and if anticholinergics are given, the treatment period should be as short as possible. Furthermore, the benefit gained in treatment adherence with once weekly dosing is lost if the patient requires treatment with an anticholinergic daily. However, such an advice on treatment with anticholinergics is not given in the SmPC, which is endorsed.

Serious adverse events

Serious adverse events include neuroleptic malignant syndrome, venous thromboembolism and possibly cardiovascular adverse events such as QT interval prolongation and torsade de pointes.

Neuroleptic malignant syndrome (NMS) is a known serious adverse event of penfluridol. The cases described in the literature illustrate that the risk for NMS is higher with concomitant use of several neuroleptics, high doses of these and recent dose changes. However, NMS can also occur without these factors. The current SmPC includes a warning in section 4.4, which is acceptable.

Venous thromboembolism is a known adverse event of antipsychotics and have also been reported with penfluridol. This risk is adequately addressed in the SmPC.

QT interval prolongation and associated cardiovascular adverse events are reported for other antipsychotics and QT interval prolongation has been noted in one penfluridol study (Gallant et al. 1974). The SmPC includes a warning regarding use in patients with cardiovascular disorders, which is endorsed.

An approximately 3-fold increased risk of cerebrovascular adverse reactions has been seen in randomised placebo-controlled clinical trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. A warning has been included in section 4.4 of the SmPC, which is endorsed.

The proposed SmPC includes a warning concerning patients with depression, due to risk of worsening of depressive symptoms. This is agreed.

Penfluridol, as all antipsychotics exerting their effect via the dopaminergic system, can interfere with prolactin excretion. No cases of hyperprolactinaemia were reported in the literature, however galactorrhoea was. The MAH presented one study in which significant increases in plasma prolactin levels were observed with penfluridol use. Increase in prolactin and its possible consequences are described in SmPC section 4.4 and 4.8.
While recent case-control data show an increased risk of breast cancer with long-term exposure to prolactin-increasing antipsychotics, no cases of breast cancer associated with penfluridol use were found in the literature or post-marketing data of Acemap. However considering the observed effect of penfluridol on prolactin, the shown increased risk of breast cancer with prolactin-increasing antipsychotics and available animal data suggesting increased risk of prolactin-dependent tumours, a warning on section 4.4 regarding patients with pre-existing hyperprolactinaemia and in patients with possible prolactin-dependent tumours is considered appropriate and has been included.

In general the adverse events reported for Acemap post-marketing reflect the safety profile as known for typical antipsychotics and as reported in the submitted literature.
It is notable that several psychotic relapses were reported after a switch from Semap to Acemap, as well as some adverse events. This illustrates that the penfluridol exposure from Acemap is on a low side as compared to Semap, and that the pharmacokinetics vary considerably between individuals. All of these cases were resolved after dose adjustment. As Semap has not been on the market for many years now, and patients will not be switched between these products, this issue is not relevant.

Special populations

There are limited data on penfluridol use in pregnant women. A prospective study followed up 27 pregnancies exposed to penfluridol, however this study also included patients exposed to haloperidol and results are presented only for the antipsychotics group as a whole. In this study, no major teratogenic risk was observed. One case of limb defect was observed after exposure to penfluridol. No other reports of such defects after penfluridol use are available. The current human data is insufficient to conclude on the teratogenic risk of penfluridol and animal studies are insufficient with respect to reproductive toxicity. Penfluridol is not recommended during pregnancy and in women of childbearing potential. This is adequately reflected in the SmPC.

Animal data suggests that penfluridol is excreted into breast milk, however there are no data in humans on achieved concentrations in nursing infants or any other safety data. The MAH refers to a publication by Ananth (1978), however this reference was not provided. The abstract concludes that penfluridol should be administered with caution in lactating women, however it is unclear whether this is based only on theoretical considerations or actual data in infants. The SmPC adequately reflects the lack of data and the decision to discontinue breastfeeding or penfluridol treatment should be made based the benefit/risk for the feeding child and therapy for the mother.

There are no safety data available specifically for children or adolescents. This is reflected in the SmPC.

Elderly patients can be more sensitive to adverse events of penfluridol. The proposed SmPC includes an advice to halve the starting dose in elderly, which is acceptable.
In addition, increased mortality has been reported in patients with dementia treated with antipsychotics. The proposed SmPC includes a statement on increased mortality in these patients, including that penfluridol is not indicated for the treatment of behavioural disorders in dementia. These are endorsed.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Acemap.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	
Important potential risks	• Prolactin-dependent tumour such as pituitary prolactinomas or breast cancer
Missing information	• Use in pregnant and lactating woman

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.7 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Semap. No new clinical studies were conducted.
Risk management is adequately addressed.
The provided data is considered sufficient to demonstrate efficacy of penfluridol in the maintenance treatment of schizophrenia. The safety profile of penfluridol is considered acceptable, since all RMS proposed amendments to the SmPC are implemented.

Well-established use has been demonstrated, and bridging from Acemap to the provided literature has been demonstrated.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.
The test consisted of: a pilot test with 5 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Penfluridol is a first generation antipsychotic of the diphenylbutylpiperidine group, with antidopaminerging mechanism of action. In this article 10a application, the applicant is seeking a marketing authorisation for 20 mg tablets, based on well-established use of penfluridol in the maintenance treatment of chronic or recurrent psychosis.

Well-established use is considered established. Semap, the innovator product registered by Janssen which is not on the market anymore, was registered in the EU in 1973, and therefore well-established use in terms of time has been fulfilled. It can also be considered that penfluridol has been used extensively, based on the available literature and the patient exposure to the applicant's own penfluridol product since 2012. The provided literature data consistently supports the efficacy of penfluridol. Concluding, all criteria for well-established are considered fulfilled.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Acemap with the reference

product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 25 July 2023.

LITERATURE REFERENCES

Ahlenius, S., Brown, R., Engel, J., & Lundborg, P. (1973). Learning deficits in 4 weeks old offspring of the nursing mothers treated with the neuroleptic drug penfluridol. *Naunyn-Schmiedeberg's Archives of Pharmacology*, 279, 31-37.

Ahlenius, S., Engel, J., Hård, E., Larsson, K., Lundborg, P., & Sinnerstedt, P. (1977). Open field behavior and gross motor development in offspring of nursing rat mothers given penfluridol. *Pharmacology Biochemistry and Behavior*, 6(3), 343-347.

Airoldi, L., Marcucci, F., Mussini, E., & Garattini, S. (1974). Distribution of penfluridol in rats and mice. *European Journal of Pharmacology*, 25(3), 291-295.

Ananth J. Side effects in the neonate from psychotropic agents excreted through breast-feeding. *Am J Psychiatry*. 1978 Jul;135(7):801-5.

Annunziato, L. A., Wuerthele, S. M., & Moore, K. E. (1978). Comparative effects of penfluridol on circling behavior and striatal dopac and serum prolactin concentrations in the rat. *European Journal of Pharmacology*, 50(3), 187-192.

Balant-Gorgia, A. E., & Balant, L. (1987). Antipsychotic drugs: clinical pharmacokinetics of potential candidates for plasma concentration monitoring. *Clinical pharmacokinetics*, 13, 65-90.

Engel, J., & Lundborg, P. (1974). Regional changes in monoamine levels and in the rate of tyrosine and tryptophan hydroxylation in 4 week old offspring of nursing mothers treated with the neuroleptic drug penfluridol. *Naunyn-Schmiedeberg's Archives of Pharmacology*, 282, 327-334.

Gallant, D.M., Mielke, D.H., Spirtes, M.A., Swanson, W.C., and Bost, R. (1974). Penfluridol: an efficacious long-acting oral antipsychotic compound. *American Journal of Psychiatry*, 131(6), 699-702.

Ito, K., Nurimoto, S., Shintomi, K., Kowa, Y., Yamamura, M., & Ishida, R. (1976). Pharmacological studies of an antipschotic agent, penfluridol.(1). The central pharmacological actions. Nihon Yakurigaku zasshi. *Folia Pharmacologica Japonica*, 72(7), 795-813.

Janssen, P. A., Niemegeers, C. J., Schellekens, K. H., Lenaerts, F. M., Verbruggen, F. J., Van Nueten, J. M., & Schaper, W. K. (1970). The pharmacology of penfluridol (R 16341) a new potent and orally long-acting neuroleptic drug. *European Journal of Pharmacology*, 11(2), 139-154.

Kuribara, H., Okuizumi, K., Shirota, M., & Tadokoro, S. (1975). Effects of penfluridol, a psychotropic agent, on operant behavior of rats. Nihon Yakurigaku zasshi. *Folia Pharmacologica Japonica*, 71(5), 491-503.

Lee, H. K., Chung, P. M., & Wang, S. C. (1978). Mechanism of antiemetic action of penfluridol in the dog. *European journal of pharmacology*, 53(1), 29-38.

Malmgren, H., Heykants, J. (1976). On the clinical pharmacology of penfluridol. *Nordisk Psykiatrisk Tidsskrift*, 30(5), 392-399.

Migdaloft, B. H., Grindel, J. M., Heykants, J. J. P., & Janssen, P. A. J. (1979). Penfluridol: a neuroleptic drug designed for long duration of action. *Drug Metabolism Reviews*, 9(2), 281-299.

Nose, T., & Takemoto, H. (1975). The effect of penfluridol and some psychotropic drugs on monoamine metabolism in central nervous system. *European Journal of Pharmacology*, 31(2), 351-359.

Ota, K. Y., Kurland, A. A., & Slotnick, V. B. (1974). Safety evaluation of penfluridol, a new long-acting oral antipsychotic agent. *Journal of Clinical Pharmacology*.

Soares, B.G.O., Silva de Lima, M. (2006). Penfluridol for schizophrenia. *Cochrane database of Systematic Reviews*, (2).

Solmi, M., Murru, A., Pacchiarotti, I., Undurraga, J., Veronese, N., Fornaro, M., ... & Carvalho, A. F. (2017). Safety, tolerability, and risks associated with first-and second-generation antipsychotics: a state-of-the-art clinical review. *Therapeutics and clinical risk management*, 757-777.

Tuan, N. M., & Lee, C. H. (2019). Penfluridol as a candidate of drug repurposing for anticancer agent. *Molecules*, 24(20), 3659.

Van der Lee, A.P., Önsesveren, I., Wierdsma, A. I., Van Westrhenen, R., Beekman, A.T., De Haan, L., Mulder, N.C. (2021). The impact of antipsychotic formulations on time to medication discontinuation in patients with schizophrenia: a Dutch registry-based retrospective cohort study. *CNS drugs*, 35, 451-460.

Vardanyan, R., & Hruby, V. (2006). *Synthesis of essential drugs*. Elsevier.

Zonnenberg, C., Bueno-de-Mesquita, J. M., Ramlal, D., & Blom, J. D. (2019). Antipsychotic-related hypothermia: five new cases. *Frontiers in psychiatry*, 10, 543.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-