SUMMARY OF PRODUCT CHARACTERISTICS

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

<Invented name> 100 mg capsules, hard

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule, hard contains 100 mg flupirtine maleate.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Capsule, hard

<Invented name> are reddish brown capsules, hard about 18 mm in length with the imprint “FLPT” and “100”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of acute pain in adults.

<Invented Name> must only be used if treatment with other analgesics (e.g. non-steroidal anti-inflammatory drugs, weak opioids) is contraindicated.

4.2 Posology and method of administration

Posology
Dosage should be adapted individually to suit the intensity of pain the patient is feeling and his or her response.

Unless instructed otherwise, 100 mg of flupirtine maleate is to be taken 3 to 4 times a day unchewed with liquid, ideally at the same intervals.

In the event of acute pain, dosage of 3 times 200 mg of flupirtine maleate per day is possible. A daily dose of 600 mg of flupirtine maleate should not be exceeded.

Flupirtine should be administered at the lowest effective dose for the shortest duration necessary to achieve adequate analgesia.

Duration of use
Duration of use is determined individually as prescribed by a doctor.

Due to the fact that flupirtine maleate is predominantly metabolised by the liver (see Section 5), in the case of longer use, regular checks must be made on the liver enzyme values.
(transaminase) and their development monitored, especially in comparison with the values before therapy in order to recognise any possible liver damage as early as possible.

The duration of treatment must not exceed 2 weeks.

**Elderly patients**
Patients over the age of 65 should take 100 mg of flupirtine maleate in the morning and in the evening at the start of therapy. Dosage can be increased depending on intensity of the pain and tolerance.

**Patients with renal insufficiency**
In the case of patients with significantly reduced renal function or hypoalbuminemia, a daily dose of 300 mg of flupirtine maleate should not be exceeded. If higher doses are necessary, these patients should be subject to careful medical supervision.

**Paediatric population**
The safety and efficacy of flupirtine in children and adolescents have not been established. **<Invented Name>** should not be used in children and adolescents under the age of 18 years.

**Method of administration**
The capsules, hard should be taken unchewed with sufficient liquid (preferably water). If possible, they should be taken with the upper body in a vertical position.

In exceptional cases, the capsules, hard can be opened and only their content taken/administered (e.g. via a tube).

Due to the very bitter taste, neutralisation of the flavour is recommended in terms of oral administration using appropriate foods (e.g. a banana).

### 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1.

In the case of patients with a risk of hepatic encephalopathy and patients with cholestasis, flupirtine maleate should not be administered as in these patients, worsening of encephalopathy or ataxia could occur.

Due to the muscle-relaxant action of flupirtine maleate, patients with myasthenia gravis should not be treated with flupirtine maleate.

Patients with pre-existing liver disease or alcohol abuse must not take **<Invented Name>**. Concomitant use of flupirtine with other drugs known to cause drug induced liver injury must be avoided (see Section 4.5).

Patients with recently overcome or actively existing tinnitus should not be treated with flupirtine maleate, as a study has shown that patients with tinnitus who are treated with flupirtine maleate could have an increased risk of the onset of increased liver enzyme values.

### 4.4 Special warnings and precautions for use

For patients with reduced liver or renal functions, checks on liver enzyme or creatinine values are indicated.

In the event of symptoms of liver damage, treatment should be discontinued.
Liver function tests must be performed at weekly intervals during treatment with <Invented Name> because increased liver enzyme levels, hepatitis and liver failure have been reported in association with flupirtine therapy. If abnormal liver function tests or clinical symptoms consistent with liver disease occur, treatment with <Invented Name> must be discontinued.

Patients should be advised to remain vigilant for any symptoms compatible with hepatic damage during treatment with <Invented Name> (e.g. loss of appetite, nausea, vomiting, abdominal pain, fatigue, dark urine, jaundice, pruritus) and to discontinue intake of <Invented Name> and to seek medical advice immediately if any such symptoms occur.

For patients over the age of 65 or with significantly reduced renal function or hypoalbuminemia, dose adjustment is necessary (see section 4.2).

When treated with flupirtine maleate, false positive findings could occur for bilirubin, urobilinogen and urine protein in urine test strips. False reactions to test methods for quantitative determination of serum bilirubin could also occur.

With higher doses, urine could be turned green in isolated cases, this however being of no clinical significance.

4.5 Interaction with other medicinal products and other forms of interaction

Flupirtine maleate may intensify the effects of alcohol and medicines which exhibit calming or muscle-relaxant properties.

Due to the high protein binding of flupirtine maleate, suppression of other simultaneously administered strong protein-bound medicines from protein binding must be counted on. The appropriate in vitro examinations have been conducted with Diazepam, Warfarin, acetylsalicylic acid, Benzylpenicillin, Digitoxin, Glibenclamid, Propranolol and Clonidine. Only for Warfarin and Diazepam did suppression of albumin binding reach a level in terms of which intensification of the effect of these medicines cannot be ruled out with simultaneous administration of flupirtine maleate.

For this reason, it is recommended that if treatment with flupirtine maleate is performed at the same time as coumarin derivatives, the quick value is checked more frequently in order to avoid any possible effect or that the coumarin dose be reduced. There is no suggestion of interactions with other anticoagulant medicines (acetylsalicylic acid among others).

Concomitant use of flupirtine with other drugs known to cause drug induced liver injury must be avoided (see Section 4.3).

If flupirtine maleate is taken at the same time as other medicines, which are also predominantly eliminated via the liver, checks on liver enzyme values should be performed in good time and regularly. Combination of flupirtine maleate with medicines containing paracetamol and carbamazepin should be avoided.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of flupirtine maleate by pregnant women. In animal studies, flupirtine maleate showed reproductive toxicity, however, no teratogenic effects, at the maternally toxic range (see Section 5.3). The potential risk for humans is unknown.

Flupirtine maleate must not be used during pregnancy unless absolutely necessary.

Breastfeeding
According to the studies available to date, a small percentage of flupirtine maleate passes into breast milk. Therefore, flupirtine maleate must not be administered during lactation unless absolutely necessary. Weaning is necessary if treatment with <product name> is absolutely required during lactation.

4.7 Effects on ability to drive and use machines

This medicine can have an effect on reaction time even if used as intended. Patients who feel sleepy or dizzy when being treated with flupirtine maleate should not drive or use machines. This applies even more so in combination with alcohol.

4.8 Undesirable effects

Adverse reactions reported as more than an isolated case are listed below, by system organ class and by frequency.

Frequency categories are defined using the following convention:

- very common (≥ 1/10)
- common (≥ 1/100 to < 1/10)
- uncommon (≥ 1/1,000 to < 1/100)
- rare (≥ 1/10,000 to < 1/1,000)
- very rare (< 1/10,000)
- not known (cannot be estimated from the available data)

In terms of controlled clinical studies as well as use of flupirtine maleate in practice in more than 1.5 million patients treated, the following side effects occurred.

<table>
<thead>
<tr>
<th>System</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Very rare</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
<td>Allergic reactions, increased body temperature</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Sleep disorders, loss of appetite, depression, restlessness/nervousness</td>
<td>confusion</td>
<td>Drug addiction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>fatigue (approx. 15 % of patients), especially at the start of therapy</td>
<td>Dizziness, tremors, headaches, increased sweating, dry mouth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Vision disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Heartburn, nausea/vomiting, stomach problems, constipation, abdominal pain, diarrhoea, flatulence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td>Transaminase</td>
<td></td>
<td></td>
<td>Hepatitis, liver</td>
<td></td>
</tr>
</tbody>
</table>
disorders | s increased | Rash, urticaria, pruritus | failure
--- | --- | --- | ---
Skin and subcutaneous tissue disorders | | | |

The undesirable effects are mostly dependent on dosage. In many cases these disappear during the course of further treatment or are reversible once therapy has ended.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In isolated cases of intentionally suicidal overdose in terms of which if up to 5g is taken, the following symptoms occur: Nausea, exhaustion, a racing heart, compulsion to cry, drowsiness, disturbed consciousness and a dry mouth.

After vomiting or therapy with forced diuresis, activated carbon and electrolyte infusions, a feeling of wellness will return within 6 to 12 hours. No life-threatening conditions have been observed.

In the event of an overdose or poisoning, due to findings from experiments on animals, central nervous phenomena as well as potential hepatotoxicity in the sense of an increased metabolic load must be counted on. Treatment must ensue symptomatically. No antidote is known.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics; other analgesics and antipyretics

ATC-Code: N02BG07

Flupirtine maleate is the prototype of the substance class SNEPCO (Selective NEuronal Potassium Channel Opener). It is a centrally effective non-opioid analgesic.

Flupirtine maleate activates G-Protein coupled inwards rectified K⁺ channels of the nerve cells. The outflow of K⁺ leads to stabilisation of the resting membrane potential, activation of the nerve cell membrane is reduced. Through this, activation of NMDA receptors is indirectly inhibited, as the Mg²⁺ block of the NMDA receptor is not lifted until depolarisation of the cell membrane (indirect NMDA receptor antagonism).

Flupirtine maleate does not bind itself in therapeutically relevant concentrations to α₁, α₂, 5HT₁, 5HT₂, Dopamin, Benzodiazepin, opiate, central muscarinic or nicotinic receptors.

This centrally effective substance results in three main effects:

**Analgesic effect**

Due to the selective opening of neuronic voltage-independent K⁺ channels and the outflow of K⁺ linked to this, the resting potential of the nerve cells becomes stabilised. The neuron is less excitable. The resulting indirect NMDA antagonism of flupirtine maleate protects the neurons against inflow of Ca²⁺. In this way, the sensitising effect of the intracellular Ca²⁺ increase is ameliorated. Forwarding of increasing nociceptive impulses is thus inhibited in the event of neuronic excitement.
\textbf{Muscle-relaxant effect}

The pharmacological effects described in the analgesic effect are functionally supported by the proven promotion of intake of Ca\textsuperscript{2+} in mitochondria in therapeutically relevant concentrations. The related inhibition of transfer of excitement to the motoneurons and corresponding effect on the interneurons leads to a muscle-relaxant effect. This does not concern an overall muscle-relaxant effect, but primarily a relaxing effect.

\textbf{Influencing of chronification processes}

Chronification processes should be understood as neuronal transmission processes and caused by the plasticity of neuronic functions.

The plasticity of neuronic functions causes a so-called "wind up" mechanism via induction of intra-cellular processes, which leads to response enhancement for the impulses which subsequently occur. The NMDA receptors are of special importance for triggering of these changes (gene expression). Their indirect blockade via flupirtine maleate causes suppression. The clinically corresponding pain chronification is counteracted via this, or in the case of existing chronification, stabilisation of the membrane potential causes promotion of "deletion" of the pain memory and thus a decrease in sensibility to pain.

5.2 Pharmacokinetic properties

After oral administration, flupirtine maleate is reabsorbed to the level of about 90\% from the gastro-intestinal tract and after rectal application to the level of 70\%.

Flupirtine maleate is metabolised in the liver to the level of about ¾ of the administered dose. During metabolism, hydrolysis (phase I reaction) leads to creation of a urethane structure and acetylation (phase II reaction) of the formed amine of the metabolite M1 (2-Amino-3-acetamino-6-[4-fluoride]-benzylamino pyridine). This metabolite has about a quarter of the analgesic effectiveness of flupirtine maleate and thus participates in the effect of flupirtine maleate.

Another metabolite is created via oxidative separation (phase I reaction) of the remaining p-fluorobenzyl and subsequent conjugation (phase II reaction) of the created p-fluorbenzoic acid with the glycine. This metabolite (M2) is biologically inactive. Which isoenzyme is involved in the (lower-level) oxidative route of degradation in priority has not been investigated to date. Only a small potential for interaction is expected for flupirtine maleate.

The majority of the dose (69\%) is excreted renally. This part is composed as follows: 27\% unaltered parent substance, 28\% metabolite M1 (acetyl metabolite), 12\% metabolite M2 (p-fluorohippuric acid); the remaining third is made up of several minor metabolites with currently unexplained structure.

A small part of the dose is excreted with bile and in the stool.

The plasma half-life is approx. 7 hours (or 10 hours for the sum of the parent substance and metabolite M1) in an area favourable for analgesics.

The plasma levels behave in a manner proportonate to the dose after administration of flupirtine maleate in the range of 50-300 mg.

In the case of older patients, a longer half-life has been observed after repeated administration (also compare Section 4.2).

5.3 Preclinical safety data

Flupirtine maleate did not produce any toxicologically relevant effects on organs or organ systems, either functionally or morphologically, in toxicological animal experiments studying pharmacodynamically optimal doses.
At very high doses, in particular with administration of the substance in acute situations, suppression of the central nervous system, as well as potential hepatotoxicity in terms of increased metabolic stress on the liver were detectable.

In acute and sub-chronic interaction studies with other drugs, in particular non-steroidal analgesics, in animals, there was no evidence of a potentiation or modification of the toxic effect of the separate components, in particular no change to the metabolic stress on the liver shown in acute and chronic studies with flupirtine maleate in two animal species (mouse and rat). The adaptation to this metabolic stress was characterized by a slight increase (within the physiological range) in liver enzyme activity, liver weight gain with weak enzyme induction and, compared with controls, a slightly elevated rate of single-cell necroses of liver cells, which were also regenerated after continued administration of the substance. The non-toxic doses determined in the chronic toxicity trials and in reproduction studies were, depending on the trial design, approximately three times higher than the maximum therapeutic daily dose intended for humans.

In vitro and in vivo studies provided no indication of a mutagenic effect.

In carcinogenicity studies on mice and rats, there was no indication of a carcinogenic potential. In the mouse study, nodal hyperplasias of liver cells developed, which can be attributed with sufficient certainty to an adaptation reaction of the cells to the metabolic stress after long-term application of high doses of flupirtine maleate.

In reproduction toxicology studies, neither the fertility of the parent animals nor the development of the offspring was affected at the maximum tolerated doses. Up to highly toxic doses, no teratogenic effects occurred.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule, hard content
Calcium hydrogen phosphate dihydrate
Copovidone
Silica, colloidal anhydrous
Magnesium stearate (Ph.Eur.)

Capsule, hard shell
Gelatine
Iron oxide red (E 172)
Titanium dioxide (E 171)
Sodium laurilsulphate
Water, purified

Printing ink
Schellac (E904)
Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years
6.4  Special precautions for storage

Do not store above 25 °C.

6.5  Nature and contents of container

White, opaque PVC-aluminium blisters with 10, 20, 30, 50, 60, 80, 100 or 200 capsules, hard.

White, opaque PVC/PVdC-aluminium blisters with 10, 20, 30, 50, 60, 80, 100 or 200 capsules, hard.

Not all pack sizes may be marketed.

6.6  Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7.  MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8.  MARKETING AUTHORISATION NUMBER

[To be completed nationally]

9.  DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: <[To be completed nationally]>
Date of latest renewal: <[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

September 2015