Bundesamt für Sicherheit im Gesundheitswesen

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Public Assessment Report

Scientific discussion

Movone 200 mg - Filmtabletten
Movone 300 mg - Filmtabletten
Movone 400 mg - Filmtabletten
Movone 200 mg Pulver zur Herstellung einer Suspension zum Einnehmen
Movone 300 mg Pulver zur Herstellung einer Suspension zum Einnehmen
Movone 400 mg Pulver zur Herstellung einer Suspension zum Einnehmen
Dexibuprofen

AT/H/0112/001-003
AT/H/0112/004-006

Date: 03.10.2016

This module reflects the scientific discussion for the approval of Movone 200 mg - Filmtabletten, Movone 300 mg - Filmtabletten, Movone 400 mg - Filmtabletten, Movone 200 mg Pulver zur Herstellung einer Suspension zum Einnehmen, Movone 300 mg Pulver zur Herstellung einer Suspension zum Einnehmen and Movone 400 mg Pulver zur Herstellung einer Suspension zum Einnehmen. The procedure was finalised at 22.07.2000 (MRP) and 02.07.2008 (DCP). For information on changes after these dates please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Movone 200 mg - Filmtabletten, Movone 300 mg - Filmtabletten, Movone 400 mg - Filmtabletten, Movone 200 mg Pulver zur Herstellung einer Suspension zum Einnehmen, Movone 300 mg Pulver zur Herstellung einer Suspension zum Einnehmen and Movone 400 mg Pulver zur Herstellung einer Suspension zum Einnehmen, from Gebro Pharma GmbH.

The product is indicated for*:*
- Symptomatic treatment for the relief of pain and inflammation associated with osteoarthritis.
- Acute symptomatic treatment of pain during menstrual bleeding (primary dysmenorrhoea).
- Symptomatic treatment of mild to moderate pain, such as muscular-skeletal pain or dental pain.

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC.

Dexibuprofen (= S(+)-ibuprofen) is the pharmacologically active enantiomer of ibuprofen, a non-selective NSAID. Its mechanism of action is thought to be due to inhibition of prostaglandin synthesis. In humans it reduces pain, inflammation and fever and reversibly inhibits ADP- and collagen- stimulated platelet aggregation.

II. QUALITY ASPECTS

II.1 Introduction

Movone 200 mg - Filmtabletten, Movone 300 mg - Filmtabletten and Movone 400 mg - Filmtabletten is a film-coated tablet which is presented in a blister strip or in a jar with dosing hole and hinged closure.

Movone 200 mg Pulver zur Herstellung einer Suspension zum Einnehmen, Movone 300 mg Pulver zur Herstellung einer Suspension zum Einnehmen and Movone 400 mg Pulver zur Herstellung einer Suspension zum Einnehmen is a powder for oral suspension which is presented in a sachet or in a bipartite sachet.

II.2 Drug Substance

The active substance in Movone is dexibuprofen. The specification of the active substance meets the current scientific requirements. The adequate quality of the active substance has been shown by submitting the appropriate control data. The stability of the active substance has been tested under ICH conditions. The results of the stability studies support the established retest-period.

II.3 Medicinal Product

Movone 200 mg - Filmtabletten, Movone 300 mg - Filmtabletten and Movone 400 mg - Filmtabletten contain the following excipients:
Tablet: Hypromellose, Microcrystalline cellulose, Carmellose calcium, Colloidal anhydrous silica, Talc.
Film-coating: Hypromellose, Titanium dioxide (E171), Glycerol triacetate, Talc, Macrogol 6000.

Movone 200 mg Pulver zur Herstellung einer Suspension zum Einnehmen, Movone 300 mg Pulver zur Herstellung einer Suspension zum Einnehmen and Movone 400 mg Pulver zur Herstellung einer Suspension zum Einnehmen contain the following excipients:
Sucrose, Citric acid, Orange flavour, Saccharin, Silica, Sodium laurilsulfate.
200 mg formulation: Each sachet contains 1.2 g sucrose.
300 mg formulation: Each sachet contains 1.8 g sucrose.
400 mg formulation: Each sachet contains 2.4 g sucrose.

The development of the product has been sufficiently made and deemed appropriate. The usage of all the excipients has been described.
The release specification includes the check of all parameters relevant to this pharmaceutical form. Appropriate data concerning the control of the finished product support the compliance with the release specifications.
The packaging of the medicinal product complies with the current legal requirements.
Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SmPC, with a shelf life of 36 months or 18 months (bipartite sachet only) when stored below 25°C.

The pharmaceutical quality of Movone has been adequately shown.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of active substance and medicinal product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The applicant has fulfilled practically all recommendations from Note for Guidance III/3501/91, “Investigation of chiral active substances“, section 5.3., “Development of a new single enantiomer from an approved racemate“. In addition to this Note for Guidance the applicant has performed a very complete program of genotoxicity testing with S(+) - ibuprofen.

III.2 Pharmacology

The data on pharmacodynamics were taken from the literature. While in vitro the inhibition of prostaglandin synthesis occurs almost exclusively via S(+) - ibuprofen, in vivo studies have shown only slight and non-significant differences in efficacy between S(+)- ibuprofen and racemic ibuprofen.

III.3 Pharmacokinetics

Pharmacokinetic investigations in normal and pregnant rats after single and repeated drug administrations were especially dealing with the phenomenon of the inversion of R(-) ibuprofen to the pharmacologically active S(+) - ibuprofen which in the rat in vivo occurs with 52 to 76 % of totally administered R(-)- ibuprofen. The other pharmacokinetic parameters of S(+)- ibuprofen are similar to those known for racemic ibuprofen.

III.4 Toxicology

In an acute toxicity study in rats, the calculated LD50 values were 422 mg/kg for S(+) - ibuprofen and 432 mg/kg for racemic ibuprofen.
In a 90-day toxicity study in rats, either S(+)- ibuprofen or racemic ibuprofen were given at doses of 0/20/60/180 mg/kg per day. The highest dose was reduced to 120 mg/kg daily due to treatment - related early deaths (due to perforating gastrointestinal ulcers). There were no statistically significant differences in toxicity between S(+)- ibuprofen and racemic ibuprofen.
In a segment II study in rats, S(+)- ibuprofen was given at doses of 0/20/60/120 mg/kg daily from day 6 to day 15 of pregnancy; a control group received 120 mg/kg racemic ibuprofen daily. S(+)- ibuprofen was devoid of any adverse effect on foetal morphology.
Racemic ibuprofen is unlikely to have any mutagenic potential in man. In a series of genotoxicity tests (Bacterial mutation assay, mammalian cell mutation assay in mouse lymphoma L5178Y cells, metaphase chromosome analysis on human lymphocytes, CHL chromosome aberration assay, mouse bone marrow micronucleus test) S(+)- ibuprofen was clearly not more potent than racemic ibuprofen with respect to any genotoxic risk.
Long - term carcinogenicity studies have not been performed with S(+)- ibuprofen.

The great extent of the in vivo R-S inversion is explaining the fact that in studies on acute toxicity, repeated dose toxicity, reproduction toxicity and genotoxicity the toxic effects of S(+)- ibuprofen were well comparable to those which are known for racemic ibuprofen, and that on a weight base at least in the rat S(+) - ibuprofen is not more toxic than racemic ibuprofen.

III.5 Discussion on the non-clinical aspects

The non-clinical part of the dossier is adequate.

IV. CLINICAL ASPECTS

IV.1 Introduction

Movone contains S(+)- ibuprofen (dexibuprofen), the dextrorotatory enantiomer of the known active substance ibuprofen (racemic ibuprofen or (RS)-ibuprofen).
Racemic ibuprofen has been used clinically for about 30 years as an effective and rather well tolerated nonsteroidal analgesic and antiinflammatory agent.
Dexibuprofen has been developed as a new pharmaceutical entity since the S(+)- enantiomer of ibuprofen is essential for the analgesic and antiphlogistic actions.
This is an application for the registration of a "single enantiomer of an approved racemate" according to the EU Note for Guidance on the Investigation of Chiral Active Substances (III/3501/91).

IV.2 Pharmacokinetics

The pharmacokinetic particular of ibuprofen is stereoselective inversion from R(-)- ibuprofen to S(+) - ibuprofen which in man occurs at an amount of about 50 %. This was confirmed in a multiple-dose study on the bioavailability of 300 mg S(+) - ibuprofen (test substance) versus 600 mg racemic ibuprofen (reference substance) film-coated tablets in 12 healthy volunteers. For S(+)- ibuprofen the test/reference ratio was 0.69 with respect to AUC(0-8 h) and 0.68 with respect to Cmax, thus closely approaching the theoretically expected value of 0.67.
After the original mutual recognition procedure a study has been conducted in which single oral doses of 300 mg S(+) - ibuprofen have been compared with 400 mg racemic ibuprofen: The overall exposure to S(+) – ibuprofen (based on the area under the curve) was equivalent between 300 mg S(+) - ibuprofen and 400 mg racemic ibuprofen.
Dose - adjusted bioequivalence and dose - linear pharmacokinetics have been demonstrated for all 3 submitted tablet strengths (200 mg, 300 mg and 400 mg). A high - fat breakfast delays Tmax of S(+)- ibuprofen from 2.1 to 2.8 hours, but has no effect on the extent of the systemic availability of S(+)- ibuprofen.

3 pharmacokinetic studies were submitted for Movone 200 mg Pulver zur Herstellung einer Suspension zum Einnehmen, Movone 300 mg Pulver zur Herstellung einer Suspension zum Einnehmen and Movone 400 mg Pulver zur Herstellung einer Suspension zum Einnehmen:
Two bioequivalence studies compared the bioavailability of Dexibuprofen 400 mg powder for oral suspension and 400 mg film-coated tablets. Bioequivalence for the extent of absorption (AUC_{0-t}, $AUC_{0-\infty}$) was shown in both studies. The C_{max} of the powder for oral suspension was about 30% higher than for the film-coated tablets; in the first study the 90% confidence interval for the ratio of C_{max} was not entirely within the predefined acceptance range of 0.7 – 1.43.

The effect of food on the absorption of the suspension formulation was studied in the third trial**.** After a standardised meal, the extent of absorption was only slightly lower; C_{max} was diminished by about one third and T_{max} delayed by 0.4 hours.

IV.3 Pharmacodynamics

Pharmacotherapeutic group: Antiinflammatory and antirheumatic products, non-steroids, propionic acid derivatives.
ATC-code: M01AE14

It is well established that the analgesic and anti-inflammatory effects of dexibuprofen arise from the non-selective inhibition of COX and the resulting reduction of prostaglandin synthesis. No new pharmacodynamic data have been submitted and none are necessary.

IV.4 Clinical efficacy

For the mutual recognition procedure the applicant submitted 3 controlled clinical studies with the market formulation:
In patients with osteoarthrosis of the hip, S(+)- ibuprofen (200 or 400 mg) was compared with racemic ibuprofen 800 mg (3 times daily for 15 consecutive days). 400 mg S(+) - ibuprofen was as effective as 800 mg racemic ibuprofen and superior to 200 mg S(+)- ibuprofen.
In women with primary dysmenorrhoea there were no differences in efficacy between 200 mg S(+)- ibuprofen, 300 mg S(+)- ibuprofen and 400 mg racemic ibuprofen, administered 3 times daily for 3 (to 5) days in a three-period crossover approach.
In patients with osteoarthritis of the knee daily doses of 900 mg S(+)- ibuprofen or 150 mg diclofenac (given in 3 single doses per day for 15 days) were equally effective in the improvement of the Lequesne Index.
Two further controlled clinical studies have been finished since the original procedure:
In patients with unilateral surgical removal of the third molar tooth in the lower jar 200 mg of S(+) – ibuprofen and 400 mg of racemic ibuprofen provided comparable pain relief. 400 mg of S(+) – ibuprofen provided better pain relief than 200 mg of S(+) – ibuprofen and 400 mg of racemic ibuprofen. This study has been the subject of a type II variation procedure which has been positively finished in April 2002.
In another clinical study which is presented for the first time clinical equivalence has been demonstrated between S(+) – ibuprofen (400 mg bid) and celecoxib (100 mg bid) over 15 days in patients with osteoarthritis of the hip.
In six further studies in patients with different indications (lumbal vertebral syndrome, rheumatoid arthritis, distortion of ankle joint, osteoarthritis of the knee, ankylosing spondylitis, osteoarthritis of the hip) a clinical trial formulation of 400 mg S(+)- ibuprofen was therapeutically equivalent to 800 mg ibuprofen (each drug given 3 times daily for 3 days to 3 weeks).

For the decentralised procedure clinical efficacy was investigated in a safety/efficacy study, a phase III, randomised, open-label, parallel group, multicentre trial. A daily dose of 800 mg of Dexibuprofen as powder for oral suspension (test) or film-coated tablets (reference) was administered to 209 osteoarthritis patients for 14±2 days. Non-inferiority of the powder for oral suspension versus the film-coated tablets was assessed in the confirmatory analysis for the primary efficacy criterion “change of the WOMAC – Index from baseline to day 3”; secondary criteria were the improvement of the WOMAC index on day 14 and a global subjective judgement of treatment efficacy.
After a repeated analysis of the trial data, including a responder-analysis according to the OMERACT-OARSI criteria, and a justification of the non-inferiority limit based on the

WOMAC index were provided, efficacy of the powder for oral suspension is regarded as sufficiently demonstrated.

IV.5 Clinical safety

Film coated tablets:
The most frequently reported adverse drug reactions of S(+)- ibuprofen are the same as those which are known for racemic ibuprofen: Gastric complaints, skin reactions, oedema, vertigo. In the clinical trials with the market formulation adverse events were noticed in 9.4 % of patients taking S(+)- ibuprofen and in 10.4 % of patients taking racemic ibuprofen. In comparative trials with an older formulation the rate of adverse events was 13.4 % in the patients treated with S(+)- ibuprofen (1200 mg daily) and 16.2 % in the patients treated with racemic ibuprofen (2400 mg daily). There are 116 documented patients who have received S(+)- ibuprofen for 12 months.
It can be concluded that the ADR profile of S(+)- ibuprofen is similar to that of racemic ibuprofen and that the rate of adverse events due to S(+)- ibuprofen is at least not higher than that induced by racemic ibuprofen. Moreover for S(+)- ibuprofen no adverse events have been reported which up to now are not known for racemic ibuprofen.

Powder for oral suspension:
Clinical safety data for the Dexibuprofen suspension formulation stem from the PK studies and from the clinical safety/efficacy study (see "IV.4 Clinical efficacy")**.** Reference is further made to the safety information available for the Dexibuprofen film-coated tablets.
In the study, the incidence of gastrointestinal (GI) treatment-related adverse events (AE) was the main safety objective and non-inferiority of the Dexibuprofen suspension formulation versus the film-coated tablets with regard to treatment-related GI-AE was assessed.
As a safety measure, the duration of administration of the Dexibuprofen powder for oral suspension was limited to 2 weeks.

IV.6 Discussion on the clinical aspects

The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

V. USER CONSULTATION

For Movone 200 mg - Filmtabletten, Movone 300 mg - Filmtabletten and Movone 400 mg – Filmtabletten, the package leaflet 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 PIL was English.
The results show that the package leaflet 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.

For Movone 200 mg Pulver zur Herstellung einer Suspension zum Einnehmen, Movone 300 mg Pulver zur Herstellung einer Suspension zum Einnehmen and Movone 400 mg Pulver zur Herstellung einer Suspension zum Einnehmen, a user consultation with target patient groups

on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to the Movone film-coated tablets (AT/H/0112/001-003/II/21). The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

For Movone 200 mg Pulver zur Herstellung einer Suspension zum Einnehmen, Movone 300 mg Pulver zur Herstellung einer Suspension zum Einnehmen and Movone 400 mg Pulver zur Herstellung einer Suspension zum Einnehmen, the applicant gave a commitment to perform a safety study and to seek scientific advice on the design of the study. The study results should be submitted by the marketing authorisation holder within 24 months after the granting of the marketing authorisation.

The pharmaceutical quality of Movone has been adequately shown.
There are no non-clinical or clinical concerns.
The benefit/risk relation is considered positive.

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product Information affected	Date of end of procedure	Approval/ non approval	Assessment report attached
Changes on the common SmPC	AT/H/0112/001-003/II/015	Y	15.04.2004	Approved	N
Renewal of the marketing authorisation	AT/H/0112/001-003/R/001	Y	07.04.2005	Approved	N
Changes to SmPC and harmonised PL	AT/H/0112/001-003/II/016	Y	29.03.2007	Approved	N
Withdrawal	AT/H/0112/004-006		25.03.2010		
Renewal of the marketing authorisation	AT/H/0112/001-003/R/002	Y	02.02.2012	Approved	N
Introduction of a new manufacturer of the active substance that is supported by an ASMF	AT/H/0112/001-003/II/021	N	17.01.2014	Approved	N
Repeat Use Procedure	AT/H/0112/001-003/E/001	N	05.06.2017	Approved	N
Update of SmPC/PIL and RMP in preparation of RUP in RO and SK	AT/H/0112/001-003/II/030/G	Y	02.10.2016	Approved	N
Update of SmPC/PIL and RMP in preparation of RUP	AT/H/0112/002/II/033/G	Y	28.01.2019	Approved	N
Repeat Use Procedure	AT/H/0112/001/E/002	N	24.09.2019	Approved	N
update of SmPC, PIL and Labelling as outcome of a repeat use procedure	AT/H/0112/001/II/036	Y	29.03.2020	Approved	N
Renewal	AT/H/112/001/R/003	N	12.11.2020	Approved	N
Update of the ASMF of the active substance manufacturer	AT/H/0112/001-003/II/050	N	25.05.2022	Approved	N