SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FORTINE (FLURBIPROFEN) 100mg Film tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film tablet contains;Flurbiprofen 100.0 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Acute or long-term treatment of symptoms of chronic rheumatic diseases such as rheumatoid arthritis, osteoarthritis and ankylosing spondylitis

Eliminating symptoms of soft tissue inflammation and bruising such as bursitis and tendinitis

Dysmenorrhea

4.2 Posology and method of administration

Unless recommended otherwise by the doctor;

-Recommended daily dose:

150 mg-200 mg in split doses.

Depending on the severity of symptoms, daily dose may increase up to total 300 mg doses.

-For menstruation pains,

At the beginning of symptoms, 100 mg; afterwards 50 mg-100 mg every 4-6 hours. Maximum daily dose is 300 mg.

4.3 Contraindications

It is contraindicated in those who are hypersensitive to Flurbiprofen.

Flurbiprofen is contraindicated in those who have asthma urticaria or other allergic reactions with aspirin or other non-steroidal anti-inflammatory drugs and who have active peptic ulcer or peptic ulcer history.

4.4 Special warnings and precautions for use

Patients who are chronically treated with non-steroidal anti-inflammatory medicines should be closely monitored considering that important gastrointestinal side effects may be observed.

As the other non-steroidal anti-inflammatory medicines, Flurbiprofen should be carefully used in patients with kidney and liver function impairment or with the history of kidney and liver diseases.

Flurbiprofen should be used carefully in patients with heart failure, hypertension and similar illnesses because of the possibility of liquid retention and edema.

Since Flurbiprofen may prolong the bleeding period, it should be carefully used especially in patients who have the potential of abnormal bleeding.

Usage in geriatric patients:
Although the pharmacokinetic of the drug does not change significantly in geriatric patients, Flurbiprofen should be used for a period as short as possible at minimum efficient dose in this patient group, because the gastrointestinal side effect risk is higher in this specific patient group.

4.5 Interaction with other medicinal products and other forms of interaction

When Flurbiprofen and aspirin are administered together, it is reported that serum concentrations of Flurbiprofen decreases by 50%. Therefore, concomitant administration of these two drugs is not recommended.

NSAI medicines including Flurbiprofen may increase effects of oral anticoagulants, and they may also increase the plasma concentrations of lithium, methotrexate and cardiac glycosides. Considering that Flurbiprofen may affect the bleeding parameters as other NSAI medicines, the drug should be used carefully in anticoagulant patients.

When Flurbiprofen is used concomitantly with ACE inhibitors, cyclosporine and diuretics, nephrotoxicity risk may increase.

Furbiprofen may decrease the efficiency of antihypertensives such as ACE inhibitors, betablockers and diuretics.

NSAI medicines may increase the efficiency of phenytoin and sulphonylurea group diuretics.

It is not appropriate to use Flurbiprofen together with any other NSAI medicine, because concomitant administration of several NSAI medicines increases the side effect risk.

Furthermore, please note that gastrointestinal bleeding risk will increase, when NSAI medicines are used together with corticoidsteroids, alcohol, biphosphonates and oxypentiphyline.

It should not be used with alcohol (gastric mucosa irritation may increase).
When the drug is taken with food, absorbance rate may decrease, but absorbance rate does not change.

It should not be used with the following plants which have antiagregant activity: caper grass, chaste tree fruit, primula, feverfew, garlic, ginger, ginkgo, aesculus, green tea, ginseng, red clover; administration of these plants may increase the antiagregant activity.

4.6 Fertility, pregnancy and lactation

Use in pregnancy:

The category of the pregnancy is C for the 1st and 2nd trimesters. If the doctor thinks that the benefit of the drug is higher than its potential risk on the fetus, the drug may be administered.

The category of the pregnancy is D for the 3rd trimester. In cases when the drug is required for the treatment of a life threatening situation in the pregnant woman, or any other drug cannot be used for the treatment of a serious disease or they are not sufficient to treat such disease, then Flurbiprofen is administered. Continuous administration of a NSAI drug during the 3rd trimester of the pregnancy is associated with the late labour, early closure of ductus arteriosus in fetus and continuous pulmonary hypertension in the new born infant.

Usage in Lactation:

The administration of Flurbiprofen is not recommended during the lactation due to the possible side effects of prostaglandin inhibitor drugs on new born babies.

4.7 Effects on ability to drive and use machines

NSAID users may experience side effects such as fatigue, sleepiness, restlessness and visual disturbances after taking the drug. Therefore, vehicles and machinery should not be used when such effects occur.

4.8 Undesirable effects

Gastrointestinal: Mostly seen side effects are gastrointestinal side effects. Following the administration of Flurbiprofen, nausea, vomiting, diarrhea, dyspepsia, abdominal pain, melena, hematemesis, ulcerative stomatitis and gastrointestinal bleeding were reported. More rarely observed side effects are gastritis, duodenal ulcer, gastric ulcer and gastrointestinal perforation.

Hypersensitivity: Hypersensitivity reactions were reported related to the treatment with NSAI medicines. Following can be mentioned among these reactions: (a) nonspecific allergic reactions and anaphylaxis; (b) asthma, deteriorative asthma, respiratory tract reactivity leading to bronchospasm or dyspnea; (c) different types of rash, itching, urticaria, purpura, angioedema and more rarely, skin reactions such as bullous erythematous (including epidermal necrolysis and erythema multiforma).

Cardiovascular: Edema is reported in relation to the NSAI treatment.
The causal relationship has not been determined certainly, and other side effects with fewer incidences are as follows:

Kidney: Nephrotoxicity of different forms including interstitial nephritis, nephrotic syndrome and renal failure.

Liver: Liver function impairment and hepatitis.

Nervous system and sense organs: Vision disorders, optic neuritis, headache, paraesthesia, depression, confusion, hallucination, tinnitus, vertigo, dizziness, fatigue, exhaustion and drowsiness.

Hematological: Trombocytopenia, neutropenia, agranulocytosis, aplastic anaemia and hemolytic anaemia.
Dermatology Photosensitivity (for other skin reactions, see the part 'hypersensitivity'). PLEASE CONSULT YOUR DOCTOR IN CASE OF AN UNXPECTED EFFE.

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 EFDA yellow Card Scheme, online at https://primaryreporting.who-umc.org/ET or toll free call 8482 to Ethiopian food and drug authority (EFDA).

4.9 Overdose

Over dosage of Flurbiprofen causes nausea, vomiting and gastrointestinal irritation.

There is no specific antidote for Flurbiprofen. If required, gastric lavage may be performed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic grup: Strong non-steroidal anti-inflammatory agent

ATC code: M01AE09

Flurbiprofen is strong non-steroidal anti-inflammatory agent which is a derivative of fenilalcanoic acid having analgesic, anti-inflammatory and antipyretic effects. It shows its effect depending on the inhibition of prostaglandin biosynthesis specifically at cyclooxygenase enzyme level and by inhibiting the sensitization of tissues against peripheral pain mediators.

5.2 Pharmacokinetic properties

In pharmacologic studies, it was reported that Flurbiprofen was efficient even at concentrations below the equilibrium level plasma levels occurred after the treatment doses.

Incidence of the side effects due to the administration of Flurbiprofen is fairly low. Most of the side effects are mild and temporary. No side effects were reported on the liver, kidney and hematopoietic systems. Flurbiprofen is absorbed in a rapid way after its oral administration, and it reaches blood peak levels approximately in 1.5 hours. Its uptake with food does not change the bioavailability of the drug. Flurbiprofen binds to serum proteins by more than 99%. Synovial fluid concentrations are lower than the plasma. Elimination half time is approximately 6 hours. Flurbiprofen is highly metabolized, and metabolization is performed mostly in liver. It is excreted from the body through urine in free and conjugated form by the rate 20% and as hidroxylated metabolites by the rate approximately 50%. Two main metabolites of Flurbiprofen are ((2-{2-floro-4-hydroxy-4-biphenyl)) and ((2-(2-floro-3-hydroxy-4-methoxy-4-biphenyl)).

Absorption: The mean oral bioavailability of flurbiprofen from ANSAID Tablets 100 mg is 96% relative to an oral solution. Flurbiprofen is rapidly and non-stereoselectively absorbed from ANSAID, with peak plasma concentrations occurring at about 2 hours (see **Table 1**).
Administration of ANSAID with either food or antacids may alter the rate but not the extent of flurbiprofen absorption. Ranitidine has been shown to have no effect on either the rate or extent of flurbiprofen absorption from ANSAID.

Distribution: The apparent volume of distribution (Vz/F) of both R- and S-flurbiprofen is approximately 0.12 L/Kg. Both flurbiprofen enantiomers are more than 99% bound to plasma proteins, primarily albumin. Plasma protein binding is relatively constant for the typical average steady-state concentrations ($\leq$ 10 μg/mL) achieved with recommended doses.
Flurbiprofen is poorly excreted into human milk. The nursing infant dose is predicted to be approximately 0.1 mg/day in the established milk of a woman taking ANSAID 200 mg/day

Metabolism: Several flurbiprofen metabolites have been identified in human plasma and urine. These metabolites include 4'-hydroxy-flurbiprofen, 3', 4'-dihydroxy-flurbiprofen, 3'-hydroxy-4'-methoxy-flurbiprofen, their conjugates, and conjugated flurbiprofen. Unlike other arylpropionic acid derivatives (eg, ibuprofen), metabolism of R-flurbiprofen to S-flurbiprofen is minimal. *In vitro* studies have demonstrated that cytochrome P450 2C9 plays an important role in the metabolism of flurbiprofen to its major metabolite, 4'-hydroxy-flurbiprofen. The 4'-hydroxy-flurbiprofen metabolite showed little anti-inflammatory activity in animal models of inflammation. Flurbiprofen does not induce enzymes that alter its metabolism.

The total plasma clearance of unbound flurbiprofen is not stereoselective, and clearance of flurbiprofen is independent of dose when used within the therapeutic range.

Excretion: Following dosing with ANSAID, less than 3% of flurbiprofen is excreted unchanged in the urine, with about 70% of the dose eliminated in the urine as parent drug and metabolites. Because renal elimination is a significant pathway of elimination of flurbiprofen metabolites, dosing adjustment in patients with moderate or severe renal dysfunction may be necessary to avoid accumulation of flurbiprofen metabolites. The mean terminal disposition half-lives (t½) of R- and S-flurbiprofen are similar, about 4.7 and 5.7 hours, respectively.
There is little accumulation of flurbiprofen following multiple doses of ANSAID.

Table 1. Mean (SD) R,S-Flurbiprofen Pharmacokinetic Parameters Normalized to a 100 mg Dose of ANSAID

Pharmacokinetic Parameter	**Normal Healthy Adults* (18 to 40 years) N=15**	**Geriatric Arthritis Patients† (65 to 83 years) N=13**	**End Stage Renal Disease Patients* (23 to 42 years) N=8**	**Alcoholic Cirrhosis Patients‡ (31 to 61 years) N=8**
Peak Concentration (Tg/mL)	14 (4)	16 (5)	9§	9§
Time of Peak Concentration (h)	1.9 (1.5)	2.2 (3)	2.3§	1.2§
Urinary Recovery of Unchanged Flurbiprofen (% of Dose)	2.9 (1.3)	0.6 (0.6)	0.02 (0.02)	NA‖
Area Under theCurve (AUC)¶ (Tg h/mL)	83 (20)	77 (24)	44§	50§
Apparent Volumeof Distribution (Vz/F, L)	14 (3)	12 (5)	10§	14§
Terminal Disposition Halflife (t½, h)	7.5 (0.8)	5.8 (1.9)	3.3#	5.4#
*100 mg single-dose † Steady-state evaluation of 100 mg every 12 hours ‡ 200 mg single-dose				

§ Calculated from mean parameter values of both flurbiprofen enantiomers || Not available ¶ AUC from 0 to infinity for single doses andfrom 0 to the end of the dosing interval for multiple-doses # Value for S-flurbiprofen	

Special Populations

Pediatric: The pharmacokinetics of flurbiprofen have not been investigated in pediatric patients.

Race: No pharmacokinetic differences due to race have been identified.

Geriatric: Flurbiprofen pharmacokinetics were similar in geriatric arthritis patients, younger arthritis patients, and young healthy volunteers receiving ANSAID Tablets 100 mg as either single or multiple doses.

Hepatic insufficiency: Hepatic metabolism may account for > 90% of flurbiprofen elimination, so patients with hepatic disease may require reduced doses of ANSAID Tablets compared to patients with normal hepatic function. The pharmacokinetics of R- and Sflurbiprofen were similar, however, in alcoholic cirrhosis patients (N=8) and young healthy volunteers (N=8) following administration of a single 200 mg dose of ANSAID tablets.

Flurbiprofen plasma protein binding may be decreased in patients with liver disease and serum albumin concentrations below 3.1 g/dL

Renal insufficiency: Renal clearance is an important route of elimination for flurbiprofen metabolites, but a minor route of elimination for unchanged flurbiprofen ($\leq$ 3% of total clearance). The unbound clearances of R- and S-flurbiprofen did not differ significantly between normal healthy volunteers (N=6, 50 mg single dose) and patients with renal impairment (N=8, inulin clearances ranging from 11 to 43 mL/min, 50 mg multiple doses). Flurbiprofen plasma protein binding may be decreased in patients with renal impairment and serum albumin concentrations below 3.9 g/dL. Elimination of flurbiprofen metabolites may be reduced in patients with renal impairment

Flurbiprofen is not significantly removed from the blood into dialysate in patients undergoing continuous ambulatory peritoneal dialysis.

5.3 Preclinical safety data

Karsinojenisite, reprodüktif ve teratoloji çalışmaları yapılmıştır. Klinik öncesi çalışmalarda, flurbiprofenin her ne kadar karsinojenik, teratojenik veya olumsuz reprodüktif etkileri bulunmamış olsa da üreme yeteneği/fertilite üzerindeki etkileri için Bölüm 4.6.'ya bakınız.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Microcrystalline cellulose pH 101
Hydroxypropyl methyl cellulose (5 cps)
Colloidal silicon dioxide
Croscarmellose sodium
Magnesium Stearate
titanium dioxide
polyethylene glycol
FD&C blue No.2 HT

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C at room temperature

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

15 or 30 film tablets in Al Foil/ PVC blister packaging in cardboard boxes with leaflets

6.6 Special precautions for disposal <and other handling>

Products that are not used or waste materials should be annihilated in line with the‘Regulation on the control of the medical waste’ and ‘Regulations on Control of thePackaging and Packaging Wastes’.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

Certificate No: 05044/5720/NMR/2018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Mar 4, 2020

10. DATE OF REVISION OF THE TEXT

September 2023