Aceclofenac, a Preferential COX-2 Inhibitor - Appraisal of Safety and Tolerability

Anu Grover1, Eknath Pawar2, G. K. Singh3, Ashok Gupta4, Anil Pareek5, Rujul Desai6, Indranil Purkait7

1 Deputy General Manager, Medical Affairs, Ipca Laboratories Ltd, Mumbai, Maharashtra, India. 2 Professor & HOD, Department of Orthopedics, Grant Government Medical College & J J Group of Hospitals, Mumbai, Maharashtra, India. 3 HOD, Era Medical College, Lucknow, Uttar Pradesh, India. 4 Senior Orthopaedic Surgeon, Dharam Hospital, Chandigarh, India. 5 President Medical Affairs & Clinical Research, Ipca Laboratories Ltd, Mumbai, Maharashtra, India. 6 Assistant Manager, Medical Affairs, Ipca Laboratories Ltd, Mumbai, Maharashtra, India. 7 Senior General Manager, Medical Affairs, Ipca Laboratories Ltd, Mumbai, Maharashtra, India.

ABSTRACT

BACKGROUND
Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly used medications to reduce inflammation and pain in clinical practice. The main concern with their use is gastrointestinal and cardiovascular side effects due to inhibition of gastroprotective prostaglandins and imbalance of prostacyclin and thromboxane respectively. NSAIDs function by inhibiting the cyclooxygenase (COX) enzymes. Evidence shows the occurrence of these side effects even with their short term use. Development of NSAID with a goal of superior or similar efficacy but with lower incidences of side effects resulted in the introduction of aceclofenac. Classified as a preferential COX-2 inhibitor, aceclofenac inhibits the COX-2 enzyme preferentially (97 %) as compared to COX-1 (46 %). Lesser inhibition of the COX-1 enzyme results in lower incidences of GI side effects. Also, due to preferential COX-2 selectivity, aceclofenac balances vascular homeostasis and thus has minimal CV risk. The diversity of COX-1 and COX-2 selectivity in NSAIDs has proven clinically important. Encouraging clinical evidence shows that aceclofenac has a favourable safety profile amongst NSAIDs. Our goal in this manuscript is to give a narrative review of clinical evidence of aceclofenac’s safety and tolerability. Based on the data, we can conclude that aceclofenac is an effective analgesic in both acute and chronic inflammatory conditions, with a comparatively low risk of gastrointestinal and cardiovascular adverse effects. This favourable tolerability profile of the drug reflects a reduction in cost associated with adverse events management, from both patient’s and healthcare provider’s perspectives.

KEY WORDS
Non-Steroidal Anti-Inflammatory Drugs, Pain, Inflammation, NSAID, COX Enzyme, Preferential COX-2 Inhibitor, Aceclofenac, Gastrointestinal Safety, Cardiac Safety.
BACKGROUND

Inflammation was one of the earliest diseases to be recognized and classified based on cardinal indications. Hippocrates, a Greek physician, treated inflammation around 3500 (400 B.C.)\(^{[1]}\). Later, Bayer introduced aspirin as the first non-steroidal anti-inflammatory drug in 1899. The exact mechanism of action of aspirin introduced in 1960s aided the development of novel anti-inflammatory drugs\(^{[2]}\). Non-steroidal anti-inflammatory drugs (NSAIDs) are the cornerstone of pain management in acute, chronic and other painful inflammatory conditions.\(^{[3]}\) Approximately 70% of people, especially in the age group of 65 years or older use NSAIDs at least once per week.\(^{[4]}\) The involvement of the cyclooxygenase (COX) enzyme in the inflammatory process is the primary target of NSAIDs.\(^{[5]}\) COX enzyme exists in its two isoforms: cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). COX-1 is responsible for the formation of gastroprotective prostaglandins (PGs) while COX-2 forms inflammatory PGs. Based on the selectivity of COX enzyme inhibition, three classes of NSAIDs have emerged: non-selective COX inhibitors also called traditional NSAIDs, selective COX-2 inhibitors, and preferential COX-2 inhibitors. Traditional/Non-selective COX inhibitors such as ibuprofen, diclofenac, piroxicam, ketorolac and ketoprofen, hinder both COX-1 and COX-2 enzymes resulting in the inhibition of gastroprotective prostaglandins, thereby causing gastrointestinal (GI) side effects. This limitation of non-selective NSAIDs leads to a shift in focus to selective COX-2 inhibitors, referred to as COXIBs like celecoxib and etoricoxib. They have shown promising anti-inflammatory activity with reduced GI side effects.\(^{[6]}\) However, there has been a concern about the cardiac safety of COXIBs. Two well-known COXIBs; rofecoxib and valdecoxib were banned or withdrawn from the market by US FDA due to their cardiac adverse effects. Rofecoxib was withdrawn in 2004 from the market due to an increased risk of myocardial infarction\(^{[7]}\) and later in the same year, a black-box warning was issued for valdecoxib due to its increased cardiovascular (CV) risk. Later, the drug was withdrawn by the manufacturer.\(^{[8]}\)

Development of NSAID with a goal of improved efficacy and lower incidences of GI as well as cardiac side effects resulted in the introduction of aceclofenac. Aceclofenac, categorized as a preferential COX-2 inhibitor, has a potent anti-inflammatory action. Several clinical studies have shown its efficacy and safety profile better in comparison with other NSAIDs. Our goal in this manuscript is to give a narrative review of clinical evidence of aceclofenac’s safety and tolerability.\(^{[9]}\)

Background of Aceclofenac

Aceclofenac, a phenylacetic acid derivative, was patented in 1983 and approved for medical use in 1992 in Spain. Since then, it is used worldwide as an effective therapeutic drug in various painful inflammatory conditions, acute as well as chronic.\(^{[10]}\) Its efficacy is well established in acute musculoskeletal pain, dental pain, low back pain, arthritis and other painful conditions encountered in clinical practice.\(^{[11]}\)\(^{[22]}\)

It is a potent inhibitor of COX, a key enzyme in the synthesis of inflammatory prostaglandins and thromboxane, with selectivity for COX-2 over COX-1 isoform. NSAIDs with a preferential COX-2 inhibition over COX-1 have less GI toxicity and fewer cardiac side effects.\(^{[22]}\) Aceclofenac showed 46% inhibition of COX-1 and 97% of COX-2 inhibition.\(^{[23]}\) COX-2 selective, partially selective, or non-selective oral NSAIDs are equally effective in controlling pain. Thus, drug choice is dictated by their safety profile, according to different risk factors, and patients’ concomitant diseases and medical conditions. The benefit-risk balance of individual NSAIDs is mainly driven by their GI and CV safety profiles.\(^{[25]}\)

Safety and Tolerability Profile of Aceclofenac

Gastrointestinal Safety

NSAID-related gastrointestinal disorders represent the 2nd largest life-threatening factor after a primary illness in patients with arthritis. NSAIDs are linked to a variety of GI side effects, including acute and severe GI symptoms. These symptoms range from superficial mucosal injury/erosions, GI irritation, dyspepsia, and abdominal pain, to the development of gastric or duodenal ulcers. GI complications such as bleeding, perforation, and blockage are severe forms of NSAID-induced adverse effects. The latter may even result in hospitalization or death.\(^{[4]}\) The prevalence of NSAID induced GI side effects is shown in Figure 1.

Clinical Evidence of GI Safety of Aceclofenac

The clinical evidence on the GI safety of aceclofenac based on the type of GI adverse events is mentioned below:

**Superior in Terms of Epigastric Discomfort, Dyspepsia and Abdominal Pain**

Gastric mucus is important as the first line of defense against luminal irritants. Studies show that about 40% of the individuals who take one NSAID can present gastric erosion. According to other studies, this prevalence can reach even...
Gastrointestinal tolerance of aceclofenac is confirmed endoscopically in 42 healthy subjects by Yanagawa et al. The authors demonstrated that aceclofenac is a promising NSAID with low potential for injuring the human gastroduodenal mucosa. They endoscopically compared mucosal damage between aceclofenac and diclofenac for 2 weeks. There was a significantly lower incidence of gastric mucosal lesions with aceclofenac as compared to diclofenac (20% vs. 50%, P < 0.05) (Figure 2A). Also, a significant increase in gastric mucosal levels of cytoprotectant hexosamine was shown with aceclofenac (32.7 mg/gm to 52.7 mg/gm, P < 0.001) which was significantly decreased with diclofenac (57.6 mg/gm to 27.22 mg/gm, P < 0.05) (Figure 2B). The mechanism of this increase is unknown, but a slight modification of the structure of diclofenac may be the reason for aceclofenac to have a preventive effect on gastric mucosal damage.

In another 10-day double-blind study, it was found that diclofenac had higher GI bleeding potential as compared to aceclofenac. Diclofenac (50 mg TID) caused a significantly greater gastrointestinal blood loss as compared to aceclofenac (100 mg BID). A large prospective, multicenter observational study complying with the safety assessment of marketed medicines (SAMM) guidelines was conducted on 10142 patients (aceclofenac n=7890; diclofenac n=2252). They were prescribed aceclofenac 100 mg bid or diclofenac 75 mg bid for 12 months. The risk of GI adverse events like dyspepsia, nausea, abdominal pain and diarrhoea was 1.3, 1.5, 1.8, and 2.5-fold higher respectively among the diclofenac-treated patients. The study established that aceclofenac was not only significantly better tolerated, but also showed greater treatment acceptability and less treatment discontinuation as compared to diclofenac (Figure 3). All this clinical evidence indicates that aceclofenac has better compliance and is a patient-friendly NSAID with good GI tolerability and safety.

GI symptoms are also the major cause of withdrawal in the treatment of NSAIDs, thereby affecting the clinical outcome of an inflammatory condition. The rates of withdrawal from treatment due to adverse events are reported to be significantly lower after aceclofenac. In comparison to ketoprofen it was 2.3 vs. 13.4%; P < 0.01 and 8.2 vs. 16.4%; P=0.027 in comparison to diclofenac. All this clinical evidence indicates that aceclofenac has better compliance and is a patient-friendly NSAID with good GI tolerability and safety.

Weaker Ulcerogenic Effect

A consequence of prostaglandin depletion is to create an environment that is conducive to peptic ulcer formation and serious GI complications. Non-selective NSAIDs like...
diclofenac, piroxicam and ketorolac are more prone to ulcer formation as well as bleeding. While COX-2 selective agents are associated with fewer GI ulcer complications, there is still an increased risk of upper gastrointestinal complications (UGIC). It is recommended by the American College of Physicians that patients with previous ulcer bleeding who require an NSAID, be treated with the combination of a PPI and a COX-2 inhibitor. But, a study reported that combination therapy with NSAIDs and proton pump inhibitors (PPIs) for two weeks causes small intestinal mucosal injury in 68% of healthy adults therefore, the mucosal injury induced by NSAIDs is not prevented by PPIs. Using GI friendly NSAID, with minimal need for PPI is thus a preferable choice. Pareek et al. conducted a 6-week, multicenter clinical study comparing aceclofenac with diclofenac, to assess their GI safety and tolerability in 591 individuals with knee osteoarthritis. The incidence and severity of GI adverse events, as well as the use of gastroprotective medications, were the major endpoints in this study. Throughout the trial, the cumulative sum of GI events in the aceclofenac treatment group was considerably lower than in the diclofenac treatment group (aceclofenac: 163 versus diclofenac: 210; P < 0.001). As the incidence of GI AEs was lower in the aceclofenac group, the consumption of GPAs (gastroprotective agents) was also significantly lower compared to the diclofenac group (P < 0.001 at all visits). The authors also observed that the need for gastroprotective agents (GPAs) increased with the increase in the duration of NSAID treatment, so their use is advised for a short period.

In a study by Grau et al. it was found that the acute gastric ulcerogenic activity of aceclofenac was about 2, 4 and 7-fold lesser than that of naproxen, diclofenac or indomethacin, respectively. This study further substantiated the safety profile of aceclofenac.

**Minimal Risk of Upper GI Bleeding/Complications**

It is reported that about 1 to 2% of NSAID users experience serious complications during treatment. Patients with a history of GI injury are at a higher risk for GI complications. A prospective observational study found that bleeding complications occurred without typical ulcer symptoms (epigastric pain or dyspepsia) in up to 80% of affected patients. The risk of upper gastrointestinal complications (UGIC) is a serious public health concern. Within the European Community's Seventh Framework Programme, the safety of non-steroidal anti-inflammatory drugs [SOS] project aimed to develop decision models for regulatory and clinical use of individual NSAIDs according to their GI and cardiovascular safety. Castellsague et al conducted a systematic review and meta-analysis of 28 observational studies to provide relative risk (RR) of UGIC of individual NSAIDs. The authors found that out of 16 NSAIDs compared, Pooled RR of UGIC was lowest with aceclofenac (1.43; 95% CI 0.65, 3.15) and highest for ketorolac (11.50; 95% CI 5.56, 23.78). The commonly used NSAIDs like diclofenac and piroxicam also had a higher relative risk (diclofenac: 3.34; 95% CI 2.79, 3.99, piroxicam: 7.43; 95% CI 5.19, 10.63) (Figure 5).

**Figure 5. Relative Risk of Upper Gastrointestinal Complications**

GI safety and patient compliance improvement have also been proven with controlled-release aceclofenac (200 mg once daily) when compared with conventional aceclofenac (100 mg twice daily). While the efficacy was equal in both groups, GI adverse effects were less in the controlled release group.

A summary of various clinical studies showing GI safety and tolerability of aceclofenac in comparison to NSAIDs is given in Table 1.
In conclusion, clinical studies have proven that aceclofenac is well-tolerated amongst the NSAIDs, with a lower incidence of GI adverse effects, reduced withdrawal rate, the minimal need for gastroprotective agents and hence a greater patient compliance. It is always advisable to respect recommended daily dose and duration of treatment and avoid its usage in high-risk patients.

Cardiac Safety

Several pathways have been hypothesised to elucidate the pathophysiology of cardiac events caused by the use of NSAIDs. The most significant mechanism is disturbed equilibrium between prostacyclin (PGI₂) and thromboxane A₂ (TXA₂). PGI₂, produced by the COX-2 enzyme, is a vasodilator and inhibitor of platelet aggregation. In contrast, thromboxane A₂ (TXA₂), produced by the COX-1 enzyme is a vasoconstrictor and mediates platelet aggregation (Figure 6). The key strategy for preserving homeostasis between TXA₂ and PGI₂ is to balance COX-1 and COX-2 inhibition. This approach will help to reduce the number of cardiac incidents caused by NSAIDs.47

Several meta-analyses, randomized controlled trials, and cohort studies have reported the cardiovascular risk associated with the use of NSAIDs. Some studies have reported increased risk even with short term NSAID use of <7 days (48), CV risk due to NSAIDs is a major concern in elderly patients and those who have co-morbidities. Using NSAIDs with minimal cardiac risk is always given a preference.

Clinical Evidence of Cardiac Safety of Aceclofenac

In data from four European countries (Netherlands, Italy, Germany and United Kingdom) covering over 10 million patients, the researchers looked at the association between the risk of hospitalization for heart failure and the use of 27 different NSAIDs, including 23 traditional NSAIDs and four selective COX-2 inhibitors. The meta-analysis in this study showed a significant association between the risks of heart failure with multiple NSAIDs. Pooled odds ratio (95% CI) observed for different NSAIDs is mentioned in the below table.

| NSAID       | Pooled odds ratio (95% CI) |
|-------------|----------------------------|
| Ketorolac   | 1.85 (1.62 to 2.12)        |
| Ibuprofen   | 1.67 (1.39 to 2.00)        |
| Indomethacin| 1.55 (1.31 to 1.83)        |
| Nabumetone  | 1.48 (1.07 to 2.06)        |
| Rofecoxib   | 1.46 (1.25 to 1.69)        |
| Piroxicam   | 1.28 (1.16 to 1.42)        |
| Diclofenac  | 1.21 (1.07 to 1.37)        |
| Ibuprofen   | 1.25 (1.07 to 1.43)        |
| Nimesulide  | 1.19 (1.14 to 1.23)        |
| Naproxen    | 1.10 (1.00 to 1.20)        |
| Meloxicam   | 1.04 (0.93 to 1.16)        |
| Ketoprofen  | 1.04 (0.96 to 1.12)        |
| Diclofenac Comb | 1.02 (0.85 to 1.22)    |
| Aceclofenac | 0.97 (0.73 to 1.38)        |
| Celecoxib   | 0.96 (0.90 to 1.02)        |

NSAIDs increased the risk of hospital admission for heart failure, even if used at medium doses. An interesting
observation regarding aceclofenac within the analyses was that it showed less risk of heart failure (pooled odds ratio 0.97 (0.73 to 1.28). The risk of hospitalization due to prior heart failure was also lesser with aceclofenac as compared to other NSAIDs.[48]

An independent research project funded by the European Commission, The Safety Of Non-Steroidal anti-inflammatory drugs (SOS) project, was designed to assess and compare the risk of cardiovascular and gastrointestinal events in users of NSAIDs and coxibs. This study found that 10 NSAIDs, including ketorolac, indomethacin, etoricoxib, rofecoxib, diclofenac and their combinations, piroxicam, ibuprofen, meloxicam, and nimesulide, significantly increased the risk of MI. Ketorolac was found to have the highest risk of MI, with an adjusted odds ratio of 2.06. (1.83 to 2.32) and was correlated with COX-2 potency, but not restricted to coxibs.

Aceclofenac was found to increase MI risk non-significantly, and the adjusted odds ratio was 1.04 (0.90 to 1.19), which was less in comparison to 17 NSAIDs. (Figure 7).[50]

![Figure 7 Association between Current Use of an Individual NSAID and Risk of AMI Compared with Past Use of Any NSAID Pooled by Meta-analysis Approach][50]

It is reported that hypertension is the most common comorbidity in osteoarthritis patients. Estimates of the prevalence of hypertension in populations of adults with OA range from 32 to 81 %.[51] While prescribing the NSAIDs to these patients, minimal/no risk is shown to be preferred. Many clinical studies and PMS data have shown that aceclofenac does not interfere with blood pressure. In a comparative clinical study of aceclofenac versus etoricoxib to assess the incidence of hypertension in rheumatoid arthritis patients, it was discovered that aceclofenac does not raise diastolic or systolic blood pressure whereas etoricoxib caused an increase in both systolic and diastolic blood pressure after 24 weeks, with an increase in DBP being statistically significant.[52]

In nutshell, the cardiovascular safety of non-selective and COX-2 selective inhibitors is controversial. An NSAID with good efficacy, good GI tolerability and minimal adverse cardiovascular effects is, therefore, a profile preferred by physicians, especially in long term usage. Aceclofenac is an anti-inflammatory and analgesic drug with preferential COX-2 inhibition, with minimal GI as well as CV risk.

Other Safety Parameters

Renal Safety

Besides GI and CV, the risk of renal complication is another concern with NSAID use. Renal prostaglandins along with other mediators help to maintain normal renal homeostasis, and when prostaglandins are inhibited by the use of NSAIDs, optimal renal functions can compensate for this decrease. More significant changes may occur in patients with prior renal dysfunction or reduced perfusion. These patients are at the greatest risk for renal side effects. Although renal events are uncommon, they can have profound consequences if the drug use is not stopped and appropriate care is not initiated. Aceclofenac has the lowest renal risk in a pharmacovigilance report when compared with other NSAIDs like diclofenac, nimesulide, naproxen, piroxicam and meloxicam.[53]

As per the prescribing information of aceclofenac, there is no evidence to modify its dosage in patients with mild renal impairment, but as with other NSAIDs caution should be exercised and renal function should be monitored in these patients. Effects on renal function are usually reversible on withdrawal but, it is contraindicated in moderate to severe renal failure.[54]

Hepatic Safety

Many clinical trials and meta-analyses have found that taking NSAIDs causes an increase in liver markers or liver transaminases.[55] Clinically visible liver impairment caused by NSAIDs is uncommon (one to ten instances per 100,000 prescriptions) and usually manifests as acute hepatitis within one to three months after commencing the medication.[56]

Clinical Evidence of Hepatic Safety of Aceclofenac

Aguédez et al. assessed the hepatotoxicity of 21 NSAIDs and non-NSAIDs such as acetaminophen. It was observed that seven NSAIDs such as ibuprofen, aspirin, naproxen, nimesulide, diclofenac, piroxicam and sulindac contributed about 99 % of cases of hepatotoxicity. In the non-NSAID group, acetaminophen is the commonest cause of intrinsic hepatotoxicity. Interestingly, aceclofenac showed less than 0.1 % of total cases of liver injury. Also, it was mentioned that crude and adjusted frequencies of aceclofenac were less among 11 NSAIDs.[57] (Table 3). In a one-year post-marketing monitoring study to assess the incidence of liver toxicity with aceclofenac, meloxicam, and rofecoxib, aceclofenac showed the lowest incidence of 0.241, 95 % CI (0.006-1.343).[58]

| Group                     | Generic Name | Percentage of Total Cases of Liver Injury | Percentage of Total Cases of Liver Injury |
|---------------------------|--------------|------------------------------------------|------------------------------------------|
| Salicylates               | Aspirin      | 6.9%                                     | 12%                                      |
|                          | Salicylate   | <0.1%                                    | <0.1%                                    |
| Acetic acid derivatives   | Aceclofenac  | <0.1%                                    | <0.1%                                    |
|                          | Acemetacin   | <0.1%                                    | <0.1%                                    |
|                          | Diclofenac   | 19.5%                                    | 34.1%                                    |
|                          | Indomethacin | <0.1%                                    | <0.1%                                    |
|                          | Ketorolac    | <0.1%                                    | <0.1%                                    |
|                          | Sulindac     | 7.1%                                     | 12.4%                                    |
| Propionic acid derivatives| Dextroprofen | <0.1%                                    | <0.1%                                    |
|                          | Ibuprofen    | 8.4%                                     | 14.6%                                    |
|                          | Ketoprofen   | <0.1%                                    | <0.1%                                    |
|                          | Naproxen     | 6.4%                                     | 11.4%                                    |
|                          | Oxaprozin    | <0.1%                                    | <0.1%                                    |
| Etoico acid derivatives   | Doxicam      | <0.1%                                    | <0.1%                                    |
|                          | Meloxicam    | <0.1%                                    | <0.1%                                    |
|                          | Piroxicam    | 5.4%                                     | 9.3%                                     |
|                          | Tenoxacin    | <0.1%                                    | <0.1%                                    |
| Selective COX-2 inhibitors| Celecoxib    | <0.1%                                    | <0.1%                                    |
|                          | Rofecoxib    | <0.1%                                    | <0.1%                                    |
|                          | Valecoxib    | <0.1%                                    | <0.1%                                    |
| Sulfonylanilides          | Nimesulide   | 3.3%                                     | 5.8%                                     |
| Non-NSAID analogues       | Acetaminophen| 42.7%                                    | -                                        |
|                          | Methamizole  | <0.1%                                    | -                                        |

Table 3. Incidence of Liver Injuries by NSAIDs[57]
Pain and inflammation are the commonly seen signs and symptoms in clinical practice. NSAIDs have become the cornerstone in the management of acute, chronic and other painful inflammatory conditions. In the selection of NSAIDs, safety is an important criterion besides pain relief. Earlier, side effects pertaining to the gastrointestinal tract were mainly looked for in NSAIDs. Currently, cardiovascular risk due to NSAIDs is a major concern, especially in elderly patients and those who have comorbidities. The benefit-risk balance of individual NSAIDs is mainly driven by their GI and CV safety profiles. Aceclofenac has gained a position amongst NSAIDs over the last two decades due to its potent or equivalent anti-inflammatory and analgesic properties as well as favourable safety profile. An independent research project by the European Commission, the Safety Of non-steroidal anti-inflammatory drugs (SOS) project, was designed to assess and compare the risk of GI and CV events in NSAID users. Based on their systematic review and meta-analysis, aceclofenac was found to be the safest.

Acknowledgement
The authors thank Dr Vivek Kumawat & Dr Apurva Jawdekar for their contribution to the literature search & drafting of the manuscript

REFERENCES

1. Rao PNP, Knaus EE. Evolution of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): cyclooxygenase (COX) Inhibition and Beyond. J Pharm Pharm Sci 1997;11(2):81-110s.
2. Brune K, Hinz B. The discovery and development of antiinflammatory drugs. Arthritis Rheum 2004;50(8):2391-9.
3. Atkinson TJ, Fudin J. Nonsteroidal Antiinflammatory Drugs for Acute and Chronic Pain. Vol. 31, Physical Medicine and Rehabilitation Clinics of North America. Phys Med Rehabil Clin N Am 2020;31(2):219-31.
4. Laine L. Gastrointestinal effects of NSAIDs and coxibs. J Pain Symptom Manage 2003;25(2 Suppl):S32-40.
5. Hatt KM, Vijapura A, Maitin IB, et al. Safety considerations in prescription of nsaid for musculoskeletal pain: a narrative review. PM and R 2018;10(12):1404-11.
6. Zarghi A, Arfaei S. Selective COX-2 inhibitors: a review of their structure-activity relationships. Iran J Pharm Res 2011;10(4):655-83.
7. Topol EJ. Failing the public health--rofecoxib, Merck, and the FDA. N Engl J Med 2004;351(17):1707-9.
8. Chou R, McDonagh MS, Nakamoto E, et al. Analgesics for osteoarthritis: an update of the 2006 comparative effectiveness review. Agency for Healthc Res Qual 2011;(38).
9. Dooley M, Spencer CM, Dunn CJ. Aceclofenac: a reappraisal of its use in the management of pain and rheumatic disease. Drugs 2001;61(9):1351-78.

[10] Legrand E. Acedofenac in the management of inflammatory pain. Expert Opin Pharmacother 2004;5(6):1347-57.
[11] Yang JH, Suk KS, Lee BH, et al. Efficacy and safety of different aceclofenac treatments for chronic lower back pain: Prospective, randomized, single center, open-label clinical trials. Yonsei Med J 2017;58(3):637-43.
[12] Ward DE, Veys EM, Bowdler JM, et al. Comparison of aceclofenac with didclofenac in the treatment of osteoarthritis. Clin Rheumatol 1995;14(6):656-62.
[13] Chalini S, Raman U. Comparative efficacy of aceclofenac and etoricoxib in post-extraction pain control: randomized control trial. Indian J Dent Res 2005;16(2):47-50.
[14] Seymour RA, Frame J, Negus TW, et al. The comparative efficacy of aceclofenac and ibuprofen in postoperative pain after third molar surgery. Br J Oral Maxillofac Surg 1998;36(5):375-9.
[15] Kornasoff D, Frerick H, Bowdler J, et al. Aceclofenac is a well-tolerated alternative to naproxen in the treatment of osteoarthritis. Clin Rheumatol 1997;16(1):32-8.
[16] Pareek A, Chandurkar N, Gupta A, et al. Aceclofenac is a well-tolerated alternative to naproxen in the treatment of osteoarthritis. Clin Rheumatol 1997;16(1):32-8.
[17] Pareek A, Chandurkar N, Chandanwale AS, et al. Aceclofenac-tizanidine in the treatment of acute low back pain: a double-blind, double-dummy, randomized, multicentric, comparative study against aceclofenac alone. Eur Spine J 2011;12(5):546-53.
[18] Martín-Mola E, Gijón-Baños J, Ansoleaga JJ. Aceclofenac in comparison to ketoprofen in the treatment of rheumatoid arthritis. Rheumatol Int 1995;15(3):111-6.
[19] Schattenkirchner M, Milachowski KA. A double-blind, multicentre, randomised clinical trial comparing the efficacy and tolerability of aceclofenac with diclofenac in patients with acute low back pain. Clin Rheumatol 2003;22(2):127-35.
[20] Letzel H, Mégard Y, Lamarca R, et al. The efficacy and safety of aceclofenac versus placebo and naproxen in women with primary dysmenorrhoea. Eur J Obstet Gynecol Reprod Biol 2006;129(2):162-8.
[21] Pareek A, Chandurkar NB, Païl RT, et al. Efficacy and safety of aceclofenac and drotaverine fixed-dose combination in the treatment of primary dysmenorrhoea: a double-blind, double-dummy, randomized comparative study with aceclofenac. Eur J Obstet Gynecol Reprod Biol 2010;152(1):86-90.
[22] Lima PVP, Fontanella V. Analgesic efficacy of aceclofenac after surgical extraction of impacted lower third molars. Int J Oral Maxillofac Surg 2006;35(6):518-21.
[23] Hinz B, Rau T, Auge D, et al. Aceclofenac spares cyclooxygenase 1 as a result of limited but sustained biotransformation to diclofenac. Clin Pharmacol Ther 2003;74(3):222-35.
[24] Schmidt M, Lambert M, Olsen AMS, et al. Cardiovascular safety of non-aspirin non-steroidal anti-inflammatory drugs: Review and position paper by the working group for Cardiovascular Pharmacotherapy of the European Society of Cardiology. Eur Heart J 2016;37(13):1015-25.
[25] Pelletier JP, Martel-Pelletier J, Rannou F, et al. Efficacy and safety of oral NSAIDs and analgesics in the management of osteoarthritis: evidence from real-life setting trials and surveys. Semin Arthritis Rheum 2016;45(4):S22-7.

[26] Ribeiro AQ, Sevalho G, César CC. The use of nonsteroidal anti-inflammatory drugs and the occurrence of gastric lesions among patients undergoing upper endoscopy in a university hospital in Brazil. Clinics 2006;61(5):409-16.

[27] Yanagawa A, Endo T, Kusakari K, Kudo T, Shimada J, Mizushima Y. Endoscopic evaluation of aceclofenac-induced gastroduodenal mucosal damage: a double-blind comparison with sodium diclofenac and placebo. Japanese J Rheumatol 1998;8(3):249-59.

[28] Huskisson EC, Irani M, Murray F. A large prospective open-label, multicentre Sammad study, comparing the safety of aceclofenac with diclofenac in patients with rheumatic disease. Eur J Rheumatol Inflamm 2000;17(1):1-7.

[29] Ward DE, Veyes EM, Bowdler JM, et al. Comparison of aceclofenac with diclofenac in the treatment of osteoarthritis. Clin Rheumatol 1999;5:14(6):656-62.

[30] Pasero G, Marcolongo R, Semi U, et al. A multi-centre, double-blind comparative study of the efficacy and safety of aceclofenac and diclofenac in the treatment of rheumatoid arthritis. Curr Med Res Opin 1995;13(6):305-15.

[31] Kornasoff D, Maisenbacher J, Bowdler J, et al. The efficacy and tolerability of aceclofenac compared to indomethacin in patients with rheumatoid arthritis. Rheumatol Int 1996;15(6):225-30.

[32] Torri G, Vignati C, Agrifoglio E, et al. Aceclofenac versus piroxicam in the management of osteoarthritis of the knee: a double-blind controlled study. Curr Ther Res 1994;55(5):576-83.

[33] Bhatt DL, Scheiman J, Abraham NS, et al ACCF/ACG/AAAA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID Use. A report of the American college of cardiology foundation task force on clinical expert consensus documents. J Am Coll Cardiol 2008;52(18):1502-17.

[34] Barkun AN, Bardou M, Kuipers EJ, et al. International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding. Ann Intern Med 2010;152(2):101-13.

[35] Maiden L, Thjodleifsson B, Seigal A, et al. Long-term effects of nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 selective agents on the small bowel: a cross-sectional capsule enteroscopy study. Clin Gastroenterol Hepatol 2007;5(9):1040-5.

[36] Pareek A, Chandurkar N. Comparison of gastrointestinal safety and tolerability of aceclofenac with diclofenac: a multicenter, randomized, double-blind study in patients with knee osteoarthritis. Curr Med Res Opin 2013;29(7):849-59.

[37] Grau M, Guasch J, Montero JL, et al. Pharmacology of the potent new non-steroidal anti-inflammatory agent aceclofenac. Arzneimittelforschung 1991;41(12):1265-76.

[38] Singh G, Ramey DR, Morfeld D, et al. Gastrointestinal tract complications of nonsteroidal anti-inflammatory drug treatment in rheumatoid arthritis: a prospective observational cohort study. Arch Intern Med 1996;156(14):1530-6.

[39] Laporte JR, Ibáñez L, VidalX, et al. Upper gastrointestinal bleeding associated with the use of NSAIDs: newer versus older agents. Drug Saf 2004;27(6):41-20.

[40] Castellsague J, Riera-Guardia N, Calingaert B, et al. Individual NSAIDs and upper gastrointestinal complications: a systematic review and meta-analysis of observational studies (the SOS Project). Drug Saf 2012;35(12):1127-46.

[41] Pareek A, Chandranwale AS, Oak J, et al. Efficacy and safety of aceclofenac in the treatment of osteoarthritis: a randomized double-blind comparative clinical trial versus diclofenac - an Indian experience. Curr Med Res Opin 2006;22(5):977-88.

[42] Patil PR, Jaid J, Palani A, et al. A comparative study of efficacy and safety of diclofenac and aceclofenac in the treatment of osteoarthritis patients. J Drug Deliv Ther 2012;2(4):139-43.

[43] Chunduri NS, Kollu T, Goteki VR, et al. Efficacy of aceclofenac and diclofenac sodium for relief of postoperative pain after third molar surgery: a randomised open label comparative study. J Pharmacothother 2013;4(2):144-5.

[44] Pasero G, Ruju G, Marcolongo R, et al. Aceclofenac versus naproxen in the treatment of ankylosing spondylitis: a double-blind, controlled study. Curr Ther Res 1999;55(7):833-42.

[45] Kornasoff D, Frerick H, Bowdler J, et al. Aceclofenac is a well-tolerated alternative to naproxen in the treatment of osteoarthritis. Clin Rheumatol 1997;16(1):32-8.

[46] Busquier MP, Cakero E, Rodriguez M, et al. Comparison of aceclofenac with piroxicam in the treatment of osteoarthritis. Clin Rheumatol 1997;16(2):154-9.

[47] Maillard M, Burnier M. Comparative cardiovascular safety of traditional nonsteroidal anti-inflammatory drugs. Expert Opin Drug Saf 2006;5(1):83-94.

[48] Bally M, Dendukuri N, Rich B, et al. Risk of acute myocardial infarction with NSAIDs in real world use: Bayesian meta-analysis of individual patient data. BMJ 2017;357:j1909.

[49] Arfè A, Scotti L, Varas-Lorenzo C, et al. Non-steroidal anti-inflammatory drugs and risk of heart failure in four European countries: nested case-control study. BMJ 2016;354:i4857.

[50] Masdeh GCM, Straatman H, Arfè A, et al. Risk of acute myocardial infarction during use of individual NSAIDs: a nested case-control study from the SOS project. PLoS One 2018;13(11):e0204746.

[51] Fallach N, Chodick G, Tirosh M, et al. Pain pharmacotherapy in a large cohort of patients with osteoarthritis: a real-world data analysis. Rheumatol Ther 2021;8(3):1129-41.

[52] Muppur A, Nandagopal A. Comparative study of Aceclofenac with Etoricoxib in degree of analgesia and assessment of incidence of hypertension and peptic ulcer in rheumatoid arthritis patients. IOSR J Dent Med Sci 2014;13(11):34-40.

[53] Lapeyre-Mestre M, Grolleau S, Montastruc JL. Adverse drug reactions associated with the use of NSAIDs: a case/noncase analysis of spontaneous reports from the
French pharmacovigilance database 2002-2006. Fundam Clin Pharmacol 2013;27(2):223-30.
[54] Aceclofenac 100 mg film-coated Tablets - Summary of Product Characteristics (SPC) - (eMC).
[55] Sriutha P, Sirichanchuen B, Permsuwan U. Hepatotoxicity of nonsteroidal anti-inflammatory drugs: a systematic review of randomized controlled trials. Int J Hepatol 2018;2018:5253623.
[56] Bolten WW. NSAIDs. In: Local treatment of inflammatory joint diseases: benefits and risks. National Institute of Diabetes and Digestive and Kidney Diseases 2015:63-70.
[57] Agúndez JAG, Lucena MI, Martínez C, et al. Assessment of nonsteroidal anti-inflammatory drug-induced hepatotoxicity. Expert Opin Drug Metab Toxicol 2011;7(7):817-28.
[58] Raber A, Heras J, Costa J, et al. Incidence of spontaneous notifications of adverse reactions with aceclofenac, meloxicam, and rofecoxib during the first year after marketing in the United Kingdom. Ther Clin Risk Manag 2007;3(2):225-30.